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THE EFFECT OF NORADRENALINE INFUSION ON THE SKIN TEMPERATURE IN HUMAN LIMBS

WITH SPECIAL REFERENCE TO THE VARIABILITY OF ACRAL CIRCULATION

BY

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PREFACE

The subject of the present study was suggested to me by Professor Väinö Seiro, M.D., Chief of the Second Surgical Clinic, Central Hospital, University of Helsinki. The work was carried out at his clinic. I am deeply indebted to Professor Seiro for the unflagging guidance and encouragement he gave me from the planning stage to the completion of the study. His inexhaustible interest in the phenomena of peripheral circulation and his critical vision have been a great support.

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Helsinki, February 1961

Arto Sivula.

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INTRODUCTION

The voluminous circulation of blood which is characteristic of the distal parts of the limbs protects these exposed portions of the body against detrimental external effects. The ability to endure cold in the hands and feet depends essentially on the response of the circulation to the vasoconstrictive influence of cold. This ability like the time taken for the blood flow in the hands and feet to recover after exposure to cold varies greatly in different persons. The sensitiveness of the blood vessels of the extremities and an increased vasoconstrictive tendency are often highly accentuated in functional disorders of the circulation in the limbs.

In clinical study of the circulation in the limbs attention is always paid to the skin temperature. A typical feature of a limb whose circulation is seriously disturbed by an obliterating arterial disease is low temperature in the distal parts. This is a very common observation also in various functional circulatory disorders. Cold hands and feet, however, often constitute a feature peculiar to some individual and it is far from always that they mean an actual disorder of the circulation.

The peripheral circulation in the limbs is largely controlled by the sympathetic nervous system. Sympathetic nervous impulses are received by the smooth muscle cells of the vascular walls through the release of noradrenaline which is the chemical transmitter liberated in the neuroeffector junctions of the sympathetic postganglionic nerves. All the reactions of the peripheral acral circulation which in every day life are evoked by environmental temperature fluctuations are governed by the function of the sympathetic nerves and the physiological presence of noradrenaline.

The starting point in the present work was to establish the pattern of circulatory reactions observed in the limbs in connection with noradrenaline infusion. It was decided to follow these responses

by means of continuous skin temperature measurements. It can be expected, then, that noradrenaline infusion affects the peripheral circulation like any physiological vasoconstrictive stimulus. Noradrenaline infusion as a standardised measure might reflect and help to clarify the functional and individual properties of the peripheral circulation of man.

REVIEW OF THE LITERATURE

VASOCONSTRICTION AND VASODILATATION

The histology of smooth muscle fibres in the media of the vascular wall was described by Kölliker (120) in 1849. He found that their relative amount varied in vessels of different types and sizes. He also demonstrated the contractility of human blood vessels by electrostimulation of the walls of arteries and veins in an amputated lower limb (121). Claude Bernard (25) noted in 1852 that division of the cervical sympathetic trunk of rabbit resulted in elevation of the temperature of the ipsilateral ear. In the same year, Brown-Sequard (27) found to the contrary that stimulation of the cervical sympathetic trunk caused vasoconstriction in rabbit ear. Periarterial sympathetic plexus was reported systematically by Henle (101) in 1871. These studies formed the foundation for the later investigation of the function of blood vessels. The methods of investigation used by physiologists and clinicians have often been indirect, such as temperature measurements, calorimetry and various modifications of the plethysmographic technique in which the volume changes in an organ or part of the body reflect the alterations in its circulation. The variations in the rate of flow of the blood and in the quantity of blood flowing through a certain vascular area also reflect indirectly vasoconstriction and vasodilatation but make possible the accurate registration which is necessary *e.g.* for the elucidation of pharmacodynamic problems. The technique worked out by Krogh (124) in 1919 in which direct observations are made on circulation in the transparent tissues of a live animal opened up new possibilities for experimental study and also for the observation of anatomical aspects. Capillary microscopy of man was also encouraged at that time; it involves making observations of the thinnest vessels of the lips, nailbeds and

conjunctiva. Angiography and the cinematographic technique associated with direct microscopy are recent aids to research.

Vasoconstriction is a state of constriction of the lumen of the blood vessels in the different parts of the circulatory system, which especially in small arteries and arterioles is subject to continuous variation. Vasoconstriction is an indication of the contractility of blood vessels which derives from the smooth muscle cells in the vessel wall. It is subject to both central and local control so that the requirements made by the organism as a whole and, on the other hand, the need of blood of the tissues and organs can be met without any major conflict arising between them. Central regulation is chiefly of nervous origin, and local control is mediated principally by chemical agents and metabolites.

The regulation of vasoconstriction was attributed by Folkow (68) to the independent activity of the muscle cells which produces the so-called basal vascular tonus. This basal tonus varies in the different areas of the vascular system. Basal tonus is slight in the cat's paw which has numerous arteriovenous shunts, while it is considerable in the blood vessels of the striated muscle tissue of the limbs (40). The activity of the smooth muscle cells is generally small in blood vessels with profuse sympathetic innervation and, conversely, vessels which show scanty vasomotor nerve fibres possess a high degree of basal tonus. In the former type of vessels the interruption of the sympathetic pathways leads to almost complete vasodilatation. This happens in man especially in the hands and feet while the vasodilator influence of sympathectomy is small in the muscles (15). The vessels are very sparsely innervated in vitally important tissues such as the brain and heart where circulation is governed by metabolic requirements through the medium of metabolites with a vasodilator effect. These vasodilator factors are counterbalanced by the pronounced basal tonus of the blood vessels. According to Folkow, the different forms of this principle also appear within the same vascular area where the arterioles are more subject to a central influence, whereas the metarterioles and precapillaries are more dependent on local factors. It has been shown that vascular reactions in the wing membrane of bat induced by nerve stimulation diminish on advancing towards the periphery and a sudden weakening occurs between the small arteries and terminal arterioles (168). On the

other hand, using rat mesoappendix, it has been shown that the reactivity of the vessels to adrenaline is in inverse ratio to the vessel diameter (5).

Our knowledge of the mechanism of vasoconstriction is still somewhat deficient. It is generally held that the contraction of the muscle fibres in the vessel wall causes vasoconstriction and the release of the muscle contraction causes vasodilatation. It has also been suggested that the contraction of muscle fibres might in some vessels lead in the initial phase of the contraction to the dilatation of the vessel, in association with the concurrent axial shortening of the vessel. This theory has been supported by the variation of the proportion of annular, helical or longitudinal bundles in the muscle fibre arrangement of the different parts of the vascular system (141, 96, 31). According to Hirsch (109), the function of smooth muscle does not involve shortening of the muscle fibres like in striated muscles. He considered that the pale epitheloid cells in the vessel walls are muscle cells in an active phase and that vasoconstriction is based on the swelling of smooth muscle cells. Vasodilatation, in Hirsch's opinion, is simply a consequence of the physical elasticity of the vascular wall.

Large and medium-sized arteries have no notable role in controlling the circulation during physiological states. Massive spasms can be encountered in them, however, in pathological conditions. The distribution of blood by the local requirements takes place in actual fact in the arterioles which have thick walls consisting of smooth muscle fibres. The nutritive function of the circulation, which serves tissue metabolism, is performed in the terminal capillary networks. »True capillaries» do not contract actively (171), but the contractile fibres in the precapillaries regulate the distribution of the blood into the capillary networks. Vasomotion also occurs in the veins, but for technical reasons it is more difficult to study.

NERVOUS CONTROL OF THE PERIPHERAL BLOOD VESSELS

SYMPATHETIC VASOCONSTRICTOR NERVES

Nervous control of the vascular function is exerted chiefly through the sympathetic, adrenergic, vasoconstrictive fibres which

enter the vessel walls everywhere in the vascular area. Arterioles, called »resistance vessels» because it is in them that the principal fall in blood pressure occurs, are richly supplied with sympathetic nerve fibres. »Capacity vessels», a term used chiefly of the veins, are also sympathetically innervated. Arteriovenous anastomoses show very profuse sympathetic innervation.

The course of sympathetic pre- and postganglionic fibres is common knowledge. The termination of postganglionic fibres in the vessel walls and their communication with the smooth muscle cells functioning as effectors is a disputed but very important question for neurovegetative phenomena. Stöhr (157) and Boeke (26) in particular have advocated the view that the terminal organ in the vegetative nervous system is a terminal reticulum with which the postganglionic sympathetic and parasympathetic fibres are connected syncytially. These workers envisaged a protoplasmic connection between the fibres of the terminal reticulum and the effector cells and on these grounds rejected the traditional neurone theory. Autonomic interstitial cells, also regarded as primitive ganglion cells, have been demonstrated in the terminal syncytium. Much evidence has been introduced in favour of their nervous structure. Meyling (136) regarded these cells as interstitial ganglion cells and suggested that there are synapses between them and postganglionic fibres. He considered that extensions of the interstitial cells formed a terminal syncytium and that this was the structure in which the chemical mediation took place. According to this school, the automaticity of smooth muscle cells is regarded as neurogenic and not myogenic, as it was understood by Folkow. Contradictory opinions have also been proffered. Hillarp (103) failed to demonstrate histologically ganglion cells in the vessel walls or syncytial arrangement of postganglionic fibres. He propounded the theory that postganglionic fibres run in a syncytium constituted by Schwann's cells which are reminiscent of ganglion cells and innervate the smooth muscle cells individually, forming functional neuro-effector units which, however, partially overlap each other when the terminal rami converge into one another's areas. Hillarp thus confirms the opinion previously introduced by some physiologists concerning the occurrence of motor units also in the smooth muscle tissue (50, 76).

The function of the vasoconstrictive sympathetic fibres is

subject to central control. The simplest reflex activity is represented by the spinal vasomotor reflexes elicited by afferent impulses. For instance, in man the stimulation of the visceral sensory nerves causes segmental vasoconstriction in the skin (4). Peripheral vasomotor tonus is maintained and regulated to a very great extent by the vasomotor centre located in the medulla oblongata (147, 154). The function of the vasomotor centre is regulated by continuous impulses from the baro- and chemoreceptors and it is subjected constantly to impulses emanating from the cerebral cortex and the hypothalamus. The vasomotor centre is nevertheless automatic, functionally independent of higher centres (6). It is formed of a network of neurone groups found in the formatio reticularis and is divided into a lateral pressor area and medial depressor area. These areas co-operate so that the depressor area transmits the inhibitory influences to the pressor area whose neurones are vasoconstrictive (75, 130, 131). The best known of the centres affecting the function of the vasoconstrictive fibres located in the hypothalamus is the »heat loss centre» which is situated in the anterior hypothalamus (53). Cortical autonomic areas seem to contain both excitor and inhibitor neurones. Vasoconstriction is produced in the blood vessels of the skin and of the splanchnic nerve area in consequence of the excitation of the motor and premotor cortex, and vasodilatation occurs concurrently in muscle vessels (134, 116). Vasomotor activity has been demonstrated in the orbital cortex and the temporal lobes in test animals and also in man (43, 42). In his investigations with cat Kennard (118) came to the conclusion that the autonomic function of the frontal and temporal lobes involved an inhibitory effect on the lower sympathetic centres. The gyrus cinguli has an area influencing the autonomic nervous system (123) from which bilateral stimulation elicits an influence on the autonomic functions in man, too (144). It is considered that this region transmits emotional manifestations and it is possible that changes in psychic activity influence via this route the sympathetic vasomotor nervous system and, thus, peripheral circulation.

SYMPATHETIC VASODILATOR FIBRES

It seems obvious in the present view that sympathetic vasodilator nerve fibres enter only striated muscles and possibly the

cardiac coronary arteries (164). They were earlier assumed to exist also in cutaneous and intestinal vessels (29). It is not impossible that in man such nerves pass to certain skin areas (47). Sympathetic vasodilative nerves have their centre in the motor cortex and the course of the fibres has been followed via the hypothalamus, mesencephalon and medulla oblongata to the spinal cord (52, 130). Sympathetic vasodilators are regarded as cholinergic and the vasodilatation induced by them can be blocked by small doses of atropine (28, 71). The functional significance of these nerves has not been clarified fully but they are assumed to increase muscular circulation in situations which call for rapid, strenuous muscular exertion. They are likewise considered to be of importance in increasing the blood flow in the initial phase of muscular effort before the metabolic mechanisms regulating blood flow have begun to operate. Sympathetic vasodilators do not transmit general circulatory reactions (164).

PARASYMPATHETIC VASODILATOR NERVES

Cranial and sacral parasympathetic nerves which transmit vasodilatation innervate only certain limited circulatory areas such as the tongue, salivary glands, external genitals and possibly the urinary bladder and rectum. The presence of vagal vasodilators in the visceral organs has not been established definitely since it is difficult to eliminate the secondary vasodilatation produced by increased tissue activity through the mediation of the products of metabolism (107). It is generally held that parasympathetic vasodilator nerves are cholinergic, although the vasodilator effect induced by them has been found to be very resistant to atropine (46). The activity of parasympathetic vasodilator nerves is obviously highly specialised and associated closely with the activity of the tissues which they innervate, and they have no role in the general regulation of the blood circulation (68).

VASODILATOR FIBRES IN THE DORSAL ROOTS

Stimulation of the dorsal roots of the spinal cord causes segmental vasodilatation in the skin (159). This involves not the activity of efferent vasodilator nerve fibres but antidromic stimula-

tion of afferent fibres. It is not a normal phenomenon but an event elicited only by a noxious stimulus. The »flare» of triple response is an example of vasodilatation elicited by an axon reflex in which there is antidromic conduction of impulses in the terminal rami of the nerves. The heat stimuli cause vasodilatation by this mechanism, too, but it has been shown that when this occurs the temperature change must be great enough to stimulate the pain fibres (41). Hence this mechanism hardly produces adaptation of the cutaneous circulation to temperature variations in normal conditions. A histamine-resembling substance has been regarded as the chemical transmitter at sensory nerve endings, but acetylcholine has also been suggested (46). Adenosine triphosphate or a related substance is also considered to be a possible transmitter (111). This view is supported by the prolonged duration of the vasodilatation elicited by the stimulation of dorsal roots compared with the duration of the vasodilatation induced by histamine and acetylcholine, and by the observation that the reaction affects only the precapillaries and not the arterioles (106). The vasodilator fibres of dorsal roots thus do not transmit central impulses at all, but possibly represent some kind of local protective mechanism *e.g.* against chilblains (68).

THE ROLE OF ADRENAL MEDULLARY HORMONES IN REGULATING THE BLOOD VESSELS

ADRENALINE AND NORADRENALINE

Oliver and Schäfer (138) noted in 1895 that suprarenal gland extract injected intravenously into the test animals caused constriction of the arterioles, a drastic elevation of blood pressure and changes in cardiac function and respiration. They also discovered that the active principle appeared only in the adrenal medulla. The active substance was isolated in 1901 by Takamine (163) who gave it the name adrenaline. In 1904, Stolz (158) synthetised adrenaline and some substances related to adrenaline, among them noradrenaline. Langley (127) noted the similarity between stimulation of the sympathetic nerves and injection of the suprarenal extract. Working from this in 1904, Elliott (54) advanced his theory of neurohumoral transmission and considered adrenaline

to be the chemical transmitter released at the endings of the sympathetic peripheral neurones. Barger and Dale (20) made a systematic study of a host of amines and noted that many of them have a sympathomimetic influence. It appeared that the sympathomimetic inhibitory effects of the catechol bases with a methylamino group, *e.g.* adrenaline, were more pronounced than the motor effects and, conversely, the motor effects of primary amines, *e.g.* noradrenaline, were more powerful than the inhibitory effects. Barger and Dale then came to the conclusion that the effects of adrenaline do not always correspond to the effects of sympathetic nervous stimulation. In 1921, Loewi (132) found that stimulation of the cardiac nerves liberated a sympathomimetic substance in frog heart, and Cannon and Uridil (38) showed in the same year that a sympathomimetic substance appeared in the circulating blood from the liver when the splanchnic nerve was stimulated in adrenalectomised cat. This agent, which is very similar to adrenaline in its action, was called »sympathin» by Cannon and Bacq (35) in 1931. Cannon and Rosenblueth (36, 37) advanced the hypothesis that the chemical transmitter of sympathetic nerves is combined in a different way in different receptors, and that the combination product may consequently be excitatory, sympathin E, or inhibitory, sympathin I. It was suggested by Bacq (12) in 1934 that sympathin E might be noradrenaline and sympathin I adrenaline. The view that »liver sympathin» is noradrenaline was supported later *e.g.* by Pinkston *et al.* (143). The physiological significance of noradrenaline was not established, however, until v. Euler (57, 58, 59, 60) in 1946 published his investigations in which he stated that it was possible to extract from different organs and from the sympathetic nerves a substance which possesses similar biological and chemical properties to noradrenaline. Furthermore, it was shown by Schmiterlöw (152) that the noradrenaline content of the blood vessel wall is in proportion to its degree of innervation. This corroborated the view that noradrenaline is the primary chemical transmitter of adrenergic nervous impulses.

Adrenaline was believed to be the only sympathomimetic substance produced by the adrenal gland until Holtz *et al.* (112), in 1947, proved that in addition to adrenaline there was an agent which resembled noradrenaline in extract of suprarenal gland. Holtz and Schümann (113) concluded that the proportion of noradrenaline

in sympathomimetic activity is 25 per cent in bovine suprarenal gland extract. Later studies confirmed these observations (63, 30, 77). Bergström *et al.* (24) isolated noradrenaline in crystalline form from adrenal gland extract in 1949. The relative proportions of noradrenaline and adrenaline in the adrenal medulla vary greatly in different animals (110, 56). Euler *et al.* (62) studied surgically removed human suprarenal glands and found 0.48 mg of adrenaline and 0.09 mg of noradrenaline per gramme of tissue. Histological studies have shown that adrenaline and noradrenaline originate in different cells in the adrenal medulla (55, 56, 104, 105). Both adrenaline and noradrenaline are liberated on stimulation of the splanchnic nerve (30). It has also been suggested that these hormones may be released independently of one another. This is indicated by selective noradrenaline secretion under the influence of a limited hypothalamic stimulation (69).

BIOLOGICAL PROPERTIES OF ADRENALINE AND NORADRENALINE

The pharmacological effects of adrenaline derive from both excitatory and inhibitory functions, whereas the effects of noradrenaline are chiefly excitatory. Intravenous adrenaline infusion administered to man at the rate of 0.15—0.30 μg/kg/min. causes a sharp increase in the cardiac output, a distinct increase in the systolic blood pressure while the diastolic pressure remains practically unchanged, a definite decrease in peripheral resistance and tachycardia. Noradrenaline, administered in the same way in a dosage of 0.11—0.40 μg/kg/min. reduces the cardiac output slightly or maintains it unchanged, causes a distinct increase in both the systolic and diastolic pressure, a pronounced increase in peripheral resistance and bradycardia (84). Similar blood pressure and heart rate changes were established by Pekkarinen and Hortling (140) and by Helve and Pekkarinen (100) with adrenaline and noradrenaline dosages of 0.2 μg/kg/min. The retarding effect of noradrenaline on the heart rate is obviously due to vagal reflex since a small dose of atropine is capable of inhibiting it (84, 160). In spite of its general vasoconstrictor activity noradrenaline, like adrenaline, dilatates coronary vessels (70, 66). Euler (61), speaking generally of the vascular effects of adrenaline and noradrenaline, said that adrenaline

is an »overall dilator» and noradrenaline an »overall constrictor». But Schaefer (151) emphasised that the difference was not qualitative but quantitative as regards the effects on the antagonistic control mechanisms, by which he meant the neural and peripheral mechanisms.

Adrenaline has a notable glycogenolytic effect and it also increases oxygen consumption, whereas with noradrenaline these metabolic influences are much weaker. The effect of a noradrenaline infusion on oxygen consumption in man (dosage 0.007–0.015 mg/min) is almost nil (149). Similar results were obtained by others (84, 23). The calorigenic effect of noradrenaline was found to be 11 times weaker than that of adrenaline in rabbit (135). Schüman (153), using rabbits, found that the increasing effect of noradrenaline on blood sugar was 10 times weaker than the comparable adrenaline effect. Bearn *et al.* (23) established that the increase in blood sugar in human peripheral blood provoked by noradrenaline infusion was a sixth of the increase elicited by adrenaline infusion. Results of the same magnitude were obtained by Helve and Pekkarinen (100). Adrenaline increases the lactic acid content of blood, but noradrenaline either fails to produce this effect or it is very weak, even in man (23, 100). Helve and Pekkarinen found, further, that the inorganic phosphate fraction of blood diminishes during adrenaline infusion but that only very small changes are noted during noradrenaline infusion.

The adrenaline- or noradrenaline-induced elevation of blood pressure disappears abruptly after the intravenous injection or infusion. Pekkarinen (139) noted that near-lethal intravenous injections of adrenaline (100–200 μg/kg) disappeared completely from the rabbit circulation in 5 min. and from the circulation of dog in 10 min. It was shown by Lund (133) that noradrenaline disappears from the blood as rapidly as adrenaline. He reckoned that sympathomimetic amines vanish from the circulation of an intact organism at the rate of 10 μg/kg/min. Perfusion experiments showed that the liver could destroy sympathomimetic amines at the rate of 10 mg/kg/min. The maximal destructive ability was 3 μg/kg/min. in a perfused hind limb of rabbit. Lund was of the opinion that destruction of adrenaline and noradrenaline in the liver occurs under the influence of amine oxidase, but that in muscles it takes place via the slower cytochrome oxidase system. It is worthy of

note that adrenaline and noradrenaline are not destroyed in the blood. Their destruction is preceded by their rapid diffusion into the tissues (139, 133). Adrenaline and noradrenaline are excreted in the urine partly free and partly conjugated. Of the adrenaline administered as an infusion, 0.5—1 per cent (65) and of noradrenaline, 1.5—4 per cent (64) was excreted in the urine.

BLOOD CIRCULATION IN THE LIMBS

There are two principal regions of circulation in the extremities of primary importance, the striated muscular tissue and the skin. The slightly vascularised bone and connective tissue have a secondary role only. Muscular tissue predominates in the proximal portions and skin is of the greatest importance in the distal parts of the limbs. The mechanisms regulating muscular and cutaneous circulation are very different.

Celander (39) studied the relationship of the components of the sympathico-adrenal system for their quantitative effect on the circulation of the hind limb muscles and paw skin of cat. He stimulated the sympathetic nerves innervating the vessels by a range of impulse frequencies within physiological limits and the adrenal nerves with the same impulse frequencies, and compared the resulting changes in peripheral resistance. Direct sympathetic nerve stimulation always proved much stronger than the humoral effect via the adrenal medulla or the effect of a corresponding dose of adrenaline or noradrenaline administered as an infusion. The vasoconstriction induced in the cutaneous vessels by the neural pathway was 10—20 times stronger than the humoral vasoconstriction. However, Celander evoked in the muscular circulation by adrenal stimulation an effect that was important from the quantitative standpoint even, *i.e.* vasodilatation which corresponded fully to the vasodilatation produced in the muscles by adrenaline infusion. Noradrenaline caused vasoconstriction in muscle in all the dosages used.

CIRCULATION IN THE MUSCLE

The blood vessels of the muscles are subject to sympathetic vasoconstrictive innervation but, as mentioned previously,

sympathetic vasodilator fibres enter these vessels. High functional requirements are made of muscular vessels for they must be capable of meeting the great demands that muscular effort places on the circulation. But it is in fact muscular action that constitutes the most powerful vasodilator stimulus to the blood vessels of the muscles. It is able to increase the blood flow of the muscle many times more than *e.g.* sympathetic denervation. This vasodilatation produced by muscular action occurs through the medium of the metabolic products which are liberated in muscular action and cause dilatation of the blood vessels (19).

The effect of adrenaline on the circulation of striated muscle is complicated. Infused in large doses, adrenaline causes vasoconstriction which, according to Celander (39), is in cat as pronounced as that induced by noradrenaline. However, administered in smaller doses (*e.g.* 0.5 μg/kg/min.) adrenaline causes a vasodilatation which is maximal for many animals. In the cat small doses of adrenaline cause sustained vasodilatation both intra-arterially and intravenously, although Duff and Swan (48) established only a transient initial vasodilatation in man after intra-arterial infusion of adrenaline. Celander consequently claimed that the vasodilator effect of adrenaline has a primary relation to muscular tissue. Adrenaline increases the formation of lactic acid in striated muscle, and lactic acid has a dilating effect on vessels. Lundholm (135) reported that the dilating effect of adrenaline on muscle vessels was attributable to its glycogenolytic effect which produces lactic acid. Celander concurred with this opinion and considered the vasodilator effect of adrenaline to be an indirect, metabolic effect whereas the vasoconstriction elicited by larger doses represents the direct, motor effect of adrenaline.

EFFECT OF ADRENALINE AND NORADRENALINE ON CIRCULATION IN THE MUSCLES OF HUMAN LIMBS

The effect of adrenaline and noradrenaline on the circulation in the muscles of human extremities has been studied by the plethysmographic technique. The parts of the forearm and the leg inserted into the plethysmograph represent chiefly the muscular tissue.

The observation was made in 1938 by Grant and Pearson (88)

that adrenaline administered in an intravenous dose of 1 μg caused increased blood flow in the leg. Allen *et al.* (8) noted in the forearm pronounced transient vasodilatation of c. 2 minutes' duration in the initial phase of adrenaline infusion (10 μg/min., for 10 minutes). It was followed by a sustained but smaller increase in the blood flow of the forearm which persisted throughout the infusion. These workers also found that transient, pronounced vasodilatation was produced by intra-arterial administration of adrenaline, too, and that it occurred also in a sympathectomised limb. Duff and Swan (48), and Whelan (166) studied the smaller, sustained vasodilatation following marked, transient vasodilatation in the forearm and leg and found that it was a regular occurrence after intravenous adrenaline infusion in a dosage of 10 μg/min. They did not, however, establish it in a sympathectomised extremity or normal extremity after intra-arterial infusion. On the other hand, Whelan did elicit this reaction in an extremity in which the nerves had been blocked acutely and even after sympathectomy for a couple of hours.

Noradrenaline has a very different effect from adrenaline on the circulation in the forearm and the leg. Noradrenaline reduced the rate of flow in the forearm and the leg (160, 18, 128, 21, 167). A noradrenaline dose of 10 μg/min. produced no increase in the blood flow even at the beginning of the infusion, but a dose of 20 μg/min. caused a very small, transient increase in the rate of flow at the beginning of the infusion (167). Transient vasodilatation has never been established in connection with intra-arterial infusion of noradrenaline. De Largy *et al.* (128), using adrenaline and noradrenaline mixtures, found that noradrenaline was able to counteract the increasing effect of adrenaline on the circulation of a muscle only when the proportion of noradrenaline in the mixture was 75 per cent.

CIRCULATION IN THE SKIN

The cutaneous circulation serves the metabolism of the skin, but it has besides a very important role in the thermal regulation of the organism as a whole. Circulation in the skin must, moreover, ensure adequate warmth especially in the acral parts of the body which are exposed to cold. These special duties of the cutaneous circulation are reflected in the anatomic arrangement and mode of action of circulation in the skin.

Cutaneous metabolism is inconsiderable and there are only few actual capillaries in the skin, 16—65 per sq.mm. of cross section as against 1000—2000 in the same area *e.g.* in the muscle (125). A characteristic of the arrangement of cutaneous circulation is the abundance of venous plexuses which occur as venous networks in the different layers of the skin. The vasculature of the distal portions of the extremities, *e.g.* the fingers, is characterised by a profusion of arteries in sharp contrast to the paucity of capillaries (165). The explanation for this is the arteriovenous shunts which occur in the distal parts of the extremities. Arteriovenous shunts are very profuse in man at the ends of the fingers and toes and in the nail-beds, and fewer in number in the proximal parts of the fingers and in the palms and soles. They are complicated in structure but the principle on which they work is, when open, to permit a flow of blood from the arterioles past the capillary network direct to the subpapillary venous plexuses of the skin. These anastomoses are regular parts of the preterminal vascular system in human hands and feet; they are located in the cutis immediately below the papillary stratum, but are encountered to some extent also deeper in the subcutis in the vicinity of the tactile corpuscles. The arterio-venous shunts which contain numerous epitheloid cells and are found in the fingers and toes are characterised by exceedingly profuse perivascular innervation which constitutes a plexus with non-medullated vegetative nerve fibres as a continuation of the peri-arterial plexus and also medullated nerve fibres from the cutaneous nerve plexuses (44). Besides human hands and feet, arteriovenous shunts have also been established in the skin of the external ear (146). The latter are considerably simpler in structure than the anastomoses encountered at the end of the limbs. Arteriovenous shunts make possible a rapid and profuse flow of blood in the terminal parts of the limbs and permit a very large-scale regulation of the circulation. Grant and Bland (86) emphasised the point that it is thanks to the opening of arteriovenous shunts that a state of warmth is maintained in the distal parts of the extremities when they are exposed to cold. Popoff (145) considered that arteriovenous shunts play a predominant role in heat regulation.

Segmental plethysmographic study has provided an answer to the quantitative relations of the circulation in different parts of the limbs. The relative proportion of skin grows increasingly on pro-

ceeding from the proximal to the distal parts of the limb with the proportion of muscle diminishing correspondingly. Of the volume of the forearm, c. 10 per cent is skin, in the finger 50 per cent (1). It is thus considered that the circulation in the distal parts of the limb represents chiefly cutaneous circulation. Abramson and Ferris (1) showed that the blood flow in the hand at 32°C is more than twice that in the forearm calculated per surface unit of the skin, even assuming that the circulation in the resting forearm as a whole represents the circulation in its skin. It has also been shown plethysmographically that the circulation in the hand is a fourth of the circulation in the fingers (82) and that the same ratio prevails between the blood flow in the foot as a whole and the toes calculated per volume unit (83). From the literature Aschoff (10) calculated that the ratio of the circulation in the forearm, hand and fingers was 1 : 5 : 10 when the upper limb was in water of 32°C, which can be regarded as normal conditions. The corresponding ratio under the influence of heat, in water of 40—45°C, was 1 : 7 : 20, and in cold 1 : 0.6 : 0.2. Thus, at rest and in normal conditions, the circulation was more profuse in the distal than in the proximal parts of the extremities and, what is more important, the adaptability of the circulation to conditions, especially to the environmental temperature, was far greater in the distal than in the proximal parts of the extremities. In his calorimetric studies, Aschoff also demonstrated that the distal parts of the limbs were able to give out considerably greater quantities of heat per surface unit than the proximal parts of the limbs. On moving from a cold to a warm environment heat dissipation increased 30-fold in the hand and 60-fold in the finger. This ability of the distal parts of the extremities and especially of the distal phalanges of the fingers to vary the amount of circulating blood so greatly was attributed by Aschoff to the existence of arteriovenous anastomoses and he considered that they reflected the great significance of the distal parts of the upper extremities and their special position in the regulation of the heat economy of the organism.

It will be clear from the foregoing how sensitively the circulation in the hand responds to variations in temperature and how great a vasoconstrictive effect cold has on the circulation in the hand. These reactions are centrally controlled via the sympathetic vasoconstrictive nerves. According to Freeman (74), the circulation of

an intact hand responds to cold in accordance with the factors affecting the heat economy of the organism through the medium of sympathetic nerves, whereas the circulation in a sympathectomised hand responds to exposure to cold only on the basis of local metabolic changes. The requirements of the thermoregulation of the organism are transmitted as variations in sympathetic tonus to the periphery and adjust the circulation in the distal parts of the extremities to a suitable level. Vascular tonus, which is almost half way between complete dilatation and complete constriction, prevails in the hands and fingers in normal conditions when room temperature is 20—23°C (82). Feet and toes, again, have a higher tonus in the same conditions and their circulation is close to the lower limit (83). Thus thermoregulatory activity is established only in the hands and the feet do not participate in it at all. The role of the feet appears only at higher environmental temperatures when the total utilisable capacity of the organism is needed to dissipate the heat.

A spontaneous rhythmic variation, even in constant conditions, is a typical feature of the peripheral acral circulation. Great spontaneous fluctuation has been established in the hand, but in the forearm and the foot it is slight (3, 2). Abramson *et al.* (3) regarded this as proof of the sensitivity of the arteriovenous shunts to impulses from the vasomotor centre. Goetz (83) considered the difference between the fingers and the toes in this respect to be ostensible only since he established a similar spontaneous variation in the circulation in the toes and fingers in suitable conditions when the feet were raised. Abramson *et al.* found that the volume of the peripheral circulation varied within the normal range much more when the water temperature in the plethysmograph was 32° than when it was 45°C. They held that this proved that vasomotor tonus fluctuates more at lower than at higher temperatures.

It has been mentioned that exposure to cold causes vasoconstriction. Exposure, to extreme cold, however, causes vasodilatation in the hands and feet. This extraordinary phenomenon was first observed by Lewis (129). He followed the temperature of the skin of the fingers when they were immersed in ice water. The finger temperature first dropped to almost 0°C but rose by several degrees 10—15 min. later. Grant and Bland (86) noted that cold-induced dilatation occurred in the extremities especially in

regions where arteriovenous shunts were abundant, such as the tips of the fingers and toes, and they correlated dilatation due to exposure to cold with the opening of arteriovenous shunts. In 1930, Grant (85) noted through direct microscopic observations that the arteriovenous shunts in rabbit ear were open in warmth and closed on cooling, but re-opened when the exposure to cold was increased. Lewis found that the ability to dilatate under the influence of cold was preserved in the limb after sympathectomy but disappeared after degeneration of the sensory nerves, and regarded cold dilatation as due to an axon reflex. Cold dilatation in the hand was studied by Aschoff (9) and Greenfield *et al.* (90, 91) by calorimetry. Aschoff found that when the hand was kept in water of 10—13°C a permanent state of vasoconstriction developed during which heat loss from the hand was 45 kcal/sq.m. per hour. In water of 8—10° and especially of 4—5°C, vasoconstriction was interrupted by abrupt vasodilatation during which the heat dissipated by the hand was 120—240 kcal/sq.m. per hour. Greenfield *et al.* found that circulation in the hand came to an almost complete standstill in water of 0—6°C but that vasodilatation set in c. 5 min. later. The heat dissipation during vasodilatation was 200 cal/100 ml/min. from the hand, 877 cal/100 ml/min. from the fingers and 2200 cal/100 ml/min. from the distal 2.8 cm of the forefinger. It has been found that the first phase of dilatation in cold water is followed by a fluctuating condition in which the finger temperature and hence the heat loss decreases and increases alternately. This was called »hunting phenomenon» by Lewis. Aschoff propounded the view that the paralysis of vasoconstrictive nerve fibres in response to cold and recovery during the warming induced by vasodilatation caused the »hunting phenomenon». He considered, however, that the accumulation of the products of metabolism in the tissues during intense cooling was more probably of greater significance for the genesis of the phenomenon. Conversely, it has been noted that dilatation in response to cold can occur as a permanent condition without any vasoconstrictive intermediate phases (32). Greenfield *et al.* (92) questioned Lewis's axon reflex theory. They demonstrated that dilatation was elicited in response to cold in cases in which the nerves of the finger were completely degenerated. These workers were of the opinion that the phenomenon was not neurogenic. When the hands are removed from ice water, after the cold-induced

dilatation an after-dilatation still follows. This after-dilatation can be delayed by keeping the hands in water of 25°C for as long as two hours between the cold water bath and their final removal from water (170).

The predominant significance of central regulation for the peripheral circulation of the limbs is also reflected in the vasodilatation caused by indirect heating. It is possible to cause vasodilatation in the hand and foot by warming the other limbs or the trunk (81, 142). Reflex vasodilatation also develops after the ingestion of a hot drink (122). The phenomenon presupposes an intact sympathetic innervation and is associated with the thermal state of both the whole organism and the periphery which together modify the vasomotor tonus of the extremities. It has been shown by Ferris *et al.* (67) that when the environmental temperature is under 21.5°C and the test subject is lightly clothed, central mechanisms tend to reduce heat loss and it requires intense warming to produce reflex vasodilatation. However, between 21.5° and 25°C the vasomotor balance is sensitive and even a slight increase in heat in some part of the body causes indirect vasodilatation in the hand. On the other hand, it has been demonstrated that if the thermal balance of the body is artificially maintained by warming the clothes, the bare hands may remain warm even when exposed to an air temperature of −35°C (148). Environmental conditions modify all other vasomotor reactions, too. This was shown as regards cold vasodilatation by Spealman (156) who used uncomfortably warm (32°C), comfortable (24°C) and uncomfortably cold (16°C) room temperatures.

Abramson and Ferris (1) made plethysmographic studies of the effect of pain, hyperventilation and mental arithmetic on the circulation in the hand and in the forearm. In the hand all these stimuli caused vasoconstriction, but in the forearm either no change or a slight increase in the circulation. The authors concluded that the arterioles of the forearm are subject to sympathetic vasoconstrictive regulation either to a very small extent only or not at all. It was also established by Grant and Pearson (88) that sensory stimuli which caused vasoconstriction in the hands failed to elicit any response in the forearm and the leg or caused vasodilatation. They were of the opinion, too, that the stimulation of limb circulation through indirect warming was reflected as a temperature rise

in the skin of the forearm only through the increased volume of blood flowing to the forearm skin from the hand along the superficial veins. Grant and Holling (87), however, using skin thermometry, noted that very marked warming of the body caused increased circulation in the skin of the forearm although the circulation had been occluded distally to the area under observation. These workers also noted that indirect heating did not cause this vasodilatation if the sympathetic pathways had been interrupted or local innervation had been blocked. They showed, moreover, that blocking of the nerves did not cause vasodilatation in the skin of the forearm of a subject previously cooled although maximal vasodilatation appeared in the fingers. They noted further that the vasodilatation in the extremities caused by body warming was weaker when the nerves were blocked. Grant and Holling concluded that the cutaneous circulation in the proximal parts of the limbs was regulated by sympathetic vasodilator innervation whereas in the distal parts the regulator was the sympathetic vasoconstrictor nerves. Doupe *et al.* (47) checked all the above investigations and showed that sweating did not contribute to these reactions. The mechanism of the active vasodilatation of the proximal cutaneous areas of the extremities has been a subject of study in the last few years. Hilton and Lewis (108) showed with cat that stimulation of the chorda tympani produces a substance in the submandibular gland which, together with plasma proteins forms bradykinin, a polypeptide with a powerful vasodilating effect. Fox and Hilton (72) established the presence of the bradykinin-forming substance in sweat collected from human forearm and later (73) in subcutaneous extracellular fluid after warming the body and already before the beginning of sweating. A vasodilator mechanism operating in the proximal parts of the limbs through the medium of bradykinin might perhaps account for the differences between the circulatory reactions of the proximal and distal cutaneous areas of the limbs (51).

EFFECT OF ADRENALINE AND NORADRENALINE ON CIRCULATION IN THE SKIN OF HUMAN LIMBS

The effect of adrenaline and noradrenaline on the circulation of human skin has been studied by plethysmography of the hand. De Largy *et al.* (128) noted that intravenous infusions of both

adrenaline and noradrenaline reduced the blood flow in the hand, and that adrenaline had the greater effect. Barcroft and Swan (19), again, found the vasoconstrictive effect of both substances to be equal when intra-arterial infusions were used. Swan (161) reported that circulation in the hand increased above the initial level after intravenous adrenaline infusion. This »after-dilatation», however, was not elicited in a sympathectomised limb or after intra-arterial infusion, which led Swan to conclude that after-dilatation was caused by a central effect. Distinct after-dilatation was established by Barcroft and Swan (19) after an adrenaline infusion of 20 μg/min. for 3 min., with the temperature of the water in the plethysmograph 33°C and the room temperature 21°C. After a similar noradrenaline infusion the circulation simply returned to its former level without any after-dilatation.

The effect of intravenous noradrenaline infusion (5—30 μg/min.) on the circulation in the hand was studied calorimetrically by Barnett *et al.* (21). They found that heat loss decreased during noradrenaline infusion and increased again after its termination. The vasoconstrictive effect was most clearly demonstrable when the vessels of the hand were in a dilated state before the infusion.

SKIN THERMOMETRY

Skin thermometry is one of the most common indirect methods used to study circulation in the extremities. It is suitable for studying qualitative changes in the circulation, but even then only in carefully controlled conditions as the skin temperature is the result of the effect of many factors. The physiological factors determining skin temperature are the amount of heat brought to the skin by the circulating blood and the heating of the skin by conduction resulting from the thermal gradient between deep and superficial tissues. Cutaneous temperature also depends on physical factors, on the heat loss from the skin by various processes which are influenced by external factors. The production of heat in the organism is the consequence of its metabolism, influenced by muscular action, ingestion of food, hormonal events such as the menstrual cycle. The relative role of the circulation in skin temperature is greatest and most sensitive in the distal portions

of the limbs. Because of its small volume the finger cools rapidly even in the deep tissues after the blood flow has ceased. The temperature of the deep muscles of the forearm may also fall fairly low, *e.g.* in a water bath of 20°C in 1 hour to 25°C and in water of 13°C down to 18°C (16). By contrast, the conduction of heat by the muscles during muscular action is reflected very readily in a temperature increase in the overlying skin (88).

Comparison of the increase in temperature in the finger and the quantity of blood circulating in it determined plethysmographically shows that at low finger temperatures a certain increase in temperature is matched by a smaller increase in blood flow than at a higher temperature, and that after the finger temperature has reached its maximum the blood flow in the finger can still increase to a fairly great extent (169). To obtain some kind of quantitative picture, Burton introduced the term »thermal circulation index». In Burton's nomogram it can be seen that *e.g.* a skin temperature change from 24° to 25°C is matched by an increase of 0.06 in the index and from 35° to 36°C by an index rise of 5.00, which agrees with the plethysmographic observation reported above. Burton emphasised, however, that the indexes can be compared with each other only when they are determined by temperature changes of the same area of skin (31).

When vasodilatation follows indirect warming of the body or blocking of the sympathetic nerves small differences are demonstrable in the temperatures of individual fingers and toes. On the hand, the thumb is the warmest and the temperature gradient between it and the little finger is 0.4°C; the gradient between the 1st and 5th toe is 0.5°C (169). The difference is more pronounced between the fingers, the wrist and the forearm, the fingers being several degrees higher. The same applies to the toes, ankle and leg. In the state of vasoconstriction the contrary temperature gradients exist, and the temperatures of the fingers and toes are the lowest. When the absolute temperatures of the extremities are used in diagnosing organic arterial diseases, for instance, each reading must be compared with the temperature of the corresponding symmetric point of the other extremity, preferably during artificially induced vasodilatation.

The temperature of the fingers and toes depends greatly on the room temperature. Roth *et al.* (150) found that the temperature

of the toes of normal subjects at 18—22°C is usually practically the same or only a little higher than the temperature of the environment while the temperature of the fingers is considerably higher. When the room temperature rises to 25—26°C the finger temperature climbs to 33—35°C but the toe temperature continues to follow the room temperature. Only when the room temperature is 28—29°C does the toe temperature begin to reach the finger temperature and at a room temperature of 31—32°C all the peripheral vessels attain their maximal vasodilatation. On the other hand, Sheard *et al.* (155), noted that at temperatures of 23—28°C the humidity of the ambient air, with a relative humidity of 35—75 per cent, had hardly any effect on the skin temperature. It has been shown (94) that the basic metabolism remains unchanged in naked persons at temperatures of 22—35°C. At a low temperature, the cutaneous temperature dropped rapidly in these subjects but the basic metabolism did not begin to increase for a couple of hours by which time the test persons felt very chilly and muscular tension and shivering occurred. Ingestion of food has been found to raise the temperature of the fingers and toes (33, 155, 11). Smoking diminishes the peripheral circulation and skin temperature. The agreeableness of the room used for the examination acts as a psychic factor affecting the circulation in the fingers (137).

Coller and Maddock (45), held that the diurnal periodicity of the metabolism of the organism was directly reflected in the cutaneous temperature of the extremities. Aschoff (11) showed calorimetrically that physical heat loss in the hands is dependent on the time of day as well as on external climatic factors and ingestion of food. The heat loss from the hand observes a 24-hour rhythm. It is at its lowest late in the afternoon and at its maximum at 1900—2300 hours. Since opinions of the diurnal periodicity which differ materially from those cited have been reported, Klüken (119) examined a large material and reviewed the results separately for different skin-thermometric types.

A thorough study was made by Gahlen and Klüken (78, 79) of the great variations in the finger temperatures of different individuals in identical external and internal conditions. They distinguished three types on the basis of whether the finger temperature followed the body temperature or room temperature or varied between the two. The cases in which the temperature of

the fingers remained high (31°C) at a room temperature of 18°C were grouped in reaction type I (homoiotherm) and the cases in which the finger temperature decreased and remained close to room temperature (20°C) in reaction type III (poikilotherm). In reaction type II were placed the persons whose finger temperature varied between these two limits (amphitherm). They considered type III to represent persons with a tendency to arteriolar constriction in the hands and to disturbances in blood distribution, and type II to represent circulatory lability. Klüken (119) noted that the diurnal temperature fluctuation in the fingers differed in the different groups. In type I, the finger temperature was at its maximum in the afternoon and at its minimum in the evening. In type II, the finger temperature fell steadily throughout the day. Type III behaved in the same way as type I, but the morning temperatures of the fingers were lower than the evening temperatures.

According to Winsor (169), the temperature reactions of the toes of a person resting at 23°C in agreeable surroundings reflect his personality. The toes of a stoic individual have a high temperature in these conditions and blocking of the posterior tibial nerve does not raise it to any appreciable extent. The toe temperature is lower in the average man but can easily be raised by taking alcohol or through indirect warming. The very low toe temperature of neurotic persons does not rise readily with alcohol or indirect warming, but it does increase after a nerve block.

Skin thermometry, especially in the acral parts of the extremities, is employed in various tests of arteriolar function, such as the cold sensitivity test, the hot-cold test, the tobacco sensitivity test (169). Heidelmann (97) examined acral arteriolar function in the following manner. He first caused vasoconstriction by placing the hands for 5 min. in water of 15°C, after which he followed the recovery of the circulation. The temperature rose again to over 25°C in 10—20 min. in cases which he regarded as representing the normal type of case. This occurred in under 10 min. in the arteriole dilatation type and not for 20 min. in the arteriole constriction type. If no spontaneous temperature climb was elicited in 30 min. the test subject was given 500 ml of 55°C water to drink and the arteriolar constriction type was further graded by the ensuing response.

THE PROBLEMS

The object of the investigation now reported was to study the reactions of the circulation in the limbs, primarily in the acral parts, to the stimulus of intravenous infusion of noradrenaline. To the best of the writer's knowledge, no corresponding studies have been made by means of skin thermometry, and in particular not with reference to the apparent individual characteristics in acral circulation. That is why in addition to the study of the effect of noradrenaline infusion on the temperature of the distal parts of the extremities in general, special attention was paid to differences in the responses of the individual subjects.

It was stated in the review of the literature that the cutaneous areas of the distal and proximal parts of the extremities differ qualitatively in their circulatory response. This led the writer to study the behaviour of the cutaneous temperature in the proximal parts of the limbs, too, during noradrenaline infusion.

The tests were performed on healthy persons, but some subjects representing different peripheral circulatory disturbances in the extremities were also studied.

The problems arising in the present work can be set out as follows:

(1) Is skin temperature in the limbs affected by the intravenous infusion of noradrenaline?

(2) If so, what is the effect in the different parts of the upper and lower limbs?

(3) Do the potential effects return after the termination of the noradrenaline infusion and if so in what way?

(4) Are there individual differences which can be considered characteristic properties of the peripheral circulation of the person under examination?

(5) What are the possible clinical observations and applications?

PRESENT INVESTIGATION

METHOD

The factors influencing vasomotion and peripheral circulation were taken into consideration in developing the method of investigation. Conditions were standardised by making all the examinations in the same room, where the effect of climatic variation was kept to a minimum. There was no window opening to the outside and the atmosphere in general was cellar-like, something that Heidelmann regarded as desirable in such investigations. The room temperature was 22—23.5°C in all the examinations and this was checked throughout each individual examination. It did not change by more than 0.5°C during each examination. This was achieved without using a cross-draught. The examinations were performed in the afternoon, 3—5 hours after the subjects had last eaten or drunk coffee. They abstained from smoking for a minimum of two hours before the beginning of the test. It was also ascertained that the test subject had no symptoms of acute infection on the day of examination and that his body temperature was normal. Each examination took about 2½ hours, divided into three phases.

First Phase. — In the first phase the subject adapted himself to the test conditions. He was placed in a supine position on the horizontal examination table. The upper limbs were denuded as far as the middle of the arm. They were placed down the sides of the body and supported on pillows in a resting position with the elbows slightly flexed. This was done to prevent the arms from tiring and growing numb during the long period of the test. When the lower limbs also were examined they were denuded to the middle of the thigh, kept extended and slightly apart on the examination table. The trunk was covered with a thin blanket, if necessary

more, the point being to ensure that the person under examination felt pleasantly warm. This condition was attained during the first phase, and the clothing was neither increased nor reduced subsequently. The subject lay immobile in this way for 1 hour before commencing the thermometry. Infusion was begun in the middle of the phase, usually in the right cubital vein, with physiological saline at the same drip rate as later in the noradrenaline infusion. The infusion rate was controlled at 5-minute intervals with a metronome. The subject was accustomed to the sound of the metronome at this phase. Skin thermometry was commenced after 1 hour, recording 3 or 4 values at intervals of 5 min. from each measuring point marked previously with a dye.

Second Phase. — The noradrenaline infusion was given in the second phase. *The noradrenaline dose was 0.2 µg per kg of body weight per minute calculated as l-noradrenaline base.* The same dosage was used by Helve and Pekkarinen (100), corresponding on the whole to the doses generally used in examining the effect of noradrenaline on the limb circulation. According to Folkow (68), a dose like this approximates physiological conditions, too. *The duration of the infusion was 30 min.* The infusion solution was always made up immediately before the examination by adding 2 mg of l-noradrenaline bitartrate to 500 ml of sterile, pyrogen-free physiological saline. The noradrenaline preparation used was »Nor-Adrenal», Orion.[1] A table was worked out for the rate of infusion, giving the number of drops for the body weight in question in each case. The calculation was based on the assumption that 16 drops equal 1 ml of the infusion solution. This was the mean of several determinations. Consequently, a person weighing 60 kg received 86 drops per minute. For very heavy persons 3 mg of l-noradrenaline bitartrate was added in 500 ml of saline, which made the rate for a subject weighing 90 kg 86 drops per minute again. A metronome was used to adjust and control the drip rate. The drip rate was controlled at 5-minute intervals. Temperature measurements were made every 5th minute throughout the second phase. The noradrenaline infusion was terminated after 30 minutes.

Third Phase. — Infusion with physiological saline solution was continued at the same rate as in the preceding phase.

[1] Orion Company, Pharmaceutical Manufacturers, Helsinki.

Temperature measurements were continued at 5-minute intervals. This phase took c. 45 min.

Skin Thermometry. — The measurements were made with an electric thermometer [1] which operates on the thermocouple principle. Mobile applicators (types H 1 and H 2) designed for skin thermometry were used for the measurements. The measurements were made at marked sites on the skin without using applicators permanently fixed on the skin. The measuring results were read from the thermometer scale to an accuracy of 0.1° and the results were usually plotted on the graph by the person acting as secretary. Skin temperatures were recorded from the following points of the limbs:

Upper limbs:
- the radial surface of the terminal phalanx of the thumb, close to the margin of the nailbed;
- the ulnar surface of the terminal phalanx of the little finger, close to the margin of the nailbed;
- the radial surface of the wrist at the styloid process of radius;
- the point in the proximal third on the radial surface of the forearm;

Lower limbs:
- the tibial surface of the terminal phalanx of the big toe, close to the margin of the nailbed;
- the point above the navicular bone on the medial surface of the ankle;
- the point on the tibial side in the superior third of the leg;
- the point on the anterior medial surface in the inferior third of the thigh.

Care was taken in choosing and marking the measuring site to ensure that it was not on or in the immediate vicinity of superficial cutaneous vein. The measuring points in the forearm, leg and thigh were in the skin above the muscle.

Changing the Infusion Fluid. — The physiological saline solution and the noradrenaline solution used in the infusion were led from their respective bottles into a Y-tube and via this by the same needle into the vein. The infusion solution was changed on passing

[1] Electric Universal Thermometer, type TE3. Electrolaboratoriet, Copenhagen.

to the following phase simply by moving the clamp from the tube of one bottle to that of another. The bottle system was kept behind a curtain so that the person under examination would not observe the procedure especially as it was performed in connection with the routine control of the rate of dripping.

Other Observations Made during the Examination. — The arterial systolic and diastolic pressure were measured in the left brachium a total of 3 times during the examination; the first time was at the end of the 1st phase, before starting the noradrenaline infusion; the second time was at the end of the 2nd phase, 5 min. before the termination of the noradrenaline infusion; the third time was at the end of the 3rd phase. The heart rate was determined several times during each phase. Observations were also made of typical changes in the colour of the skin of the face and the hands during the noradrenaline infusion and after it was terminated. The subjective sensations of the test subjects during and after the noradrenaline infusion were also noted.

Controls. — The examination conditions and the subjects examined were subjected to the control reported above. The influence of the infusion procedure as such in the administration of noradrenaline was eliminated by giving the subjects infusions of mere physiological saline before and after noradrenaline. However, to ascertain the role of psychic factors a test was performed in which no noradrenaline was used on 6 subjects who also participated in the noradrenaline tests. For this test they were given only physiological saline solution alternately from 2 bottles. All the measures and manipulations carried out in the investigation proper were performed in these examinations and the test subjects believed that they were being given noradrenaline as on the previous occasion.

SERIES

The series was divided into two groups. The larger group consisted of healthy normal subjects, 44 in all, of which 21 were women and 23 men. With a few exceptions, they were young adults. All of them had a permanent job or were studying. A total of 55 noradrenaline infusion studies were made on these normal persons, together with thermometry of the upper limbs on each

occasion. Skin thermometry of the lower limbs was simultaneously performed in 32 experiments. Furthermore, a control examination with physiological saline infusion alone was performed on 6 persons of this group. There was no selection of the normal series as regards general temperature of the hands and feet, or any such consideration; the only requirement was that the subjects were healthy and able-bodied. None of the women was pregnant.

In addition to the normal series, a small group of patients with various circulatory disorders and diseases of the extremities was studied. This consisted of 11 persons on whom a total of 14 noradrenaline examinations were made. Temperature changes in the upper limbs were measured in all the subjects in this group and the temperature of the lower limbs was measured in 11 examinations.

The series as a whole thus comprised 55 subjects on whom a total of 69 noradrenaline infusion examinations were made.

As a parallel investigation the arteriolar function of the fingers was studied by Heidelmann's method in 19 subjects of the normal series and 1 subject of the group with circulatory disorders.

RESULTS

SKIN TEMPERATURE CHANGES IN THE LIMBS FOLLOWING NORADRENALINE INFUSION

FINGERS

The temperature changes in the fingertips in connection with noradrenaline infusion were interesting and surprising since they were far from consistent at least at first glance. The temperature usually fell at the beginning of noradrenaline infusion owing to the vasoconstrictive influence of the drug. In a typical case (Fig. 1) the temperature drop continued and persisted throughout the infusion. When the infusion ended the temperature rose rapidly, often above the starting temperature.

The temperature curves obtained from the fingertips were not often like this, however. The following deviations from this »basic curve» were recorded.

(i) The initial temperature, *i.e.* the fingertip temperature at the end of the 1st phase of the examination could be practically as

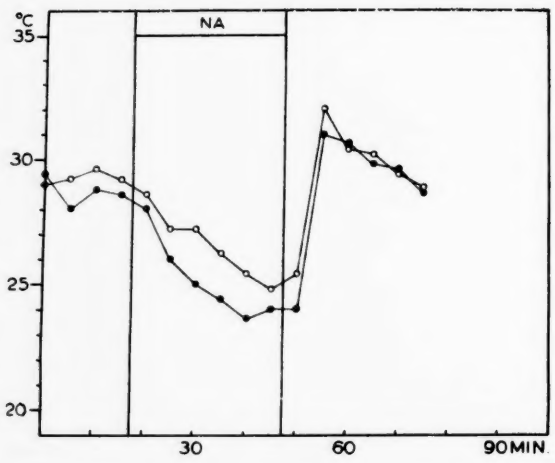

Fig. 1. — Chart showing how the fingertip temperature falls during the noradrenaline infusion (0.2 μg/kg/min., for 30 min.). The principal decrease is in the first 15—20 min. of the infusion. A rapid and sharp temperature increase occurs within 5—10 min. of the termination of the infusion. Reaction type II (Cf. p. 68).

Case No. 11 a (a woman of 21). Room temperature 22.0°C.

O—O—O right thumb; ●—●—● left little finger.

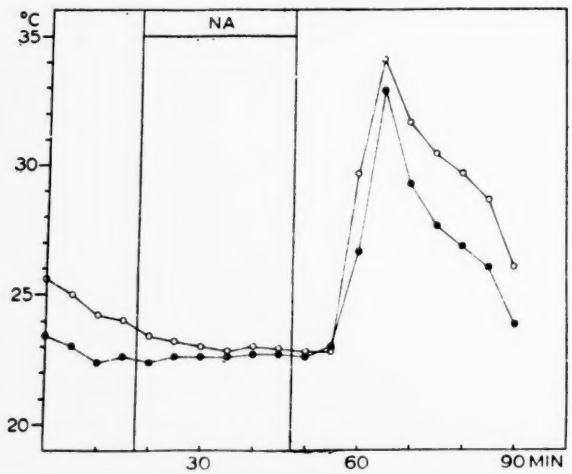

Fig. 2. — Chart of the fingertip temperature in which no notable drop is observed during the noradrenaline infusion (0.2 μg/kg/min., for 30 min.) as the initial temperature is low. Strong warming begins c. 10 min. after the infusion. Reaction type II.

Case No. 5 a (a woman of 22). Room temperature 23.0°C.

O—O—O right thumb; ●—●—● left thumb.

low as the room temperature. When this was so, the temperature could no longer fall during the noradrenaline infusion. There was in these cases considerable vasoconstriction in the fingers initially and it was not possible by skin thermometry to demonstrate any increase in vasoconstriction during the noradrenaline infusion. Fig. 2 shows an example of such a case.

(ii) Noradrenaline-induced vasoconstriction could be relieved in the different phases of the examination, and this was seen as a sudden temperature increase. The temperature drop occurring at the beginning of the noradrenaline infusion might be interrupted during the noradrenaline infusion and the temperature might begin to rise while the infusion was still in progress. The temperature curve in such a case would be biphasic at the 2nd phase of the examination, as can be seen in Fig. 3. If, by contrast, the

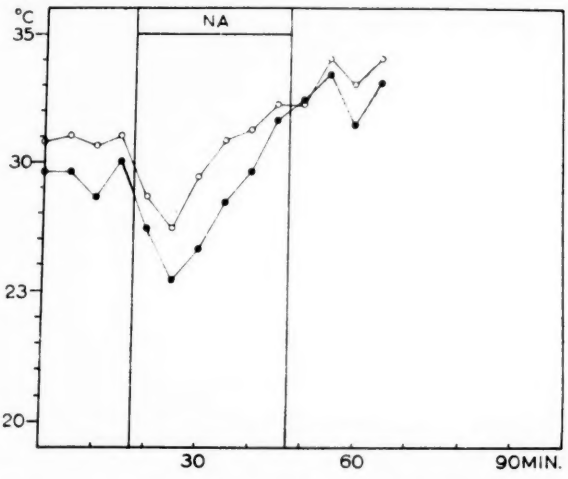

Fig. 3. — The fingertip temperature begins to fall on starting the noradrenaline infusion (0.2 μg/kg/min., for 30 min.) but after c. 10 min. of infusion begins to rise again. There is another increase after the termination of the noradrenaline infusion (especially in the thumb). Reaction type I.

Case No. 36 (a woman of 22). Room temperature 22.6°C.

O—O—O right thumb; ●—●—● right little finger.

temperature fell steadily in the fingertips throughout the noradrenaline infusion the opposite changes would take place in the 3rd phase of the examination. The fingertip temperature could rise immediately after the termination of the noradrenaline infusion

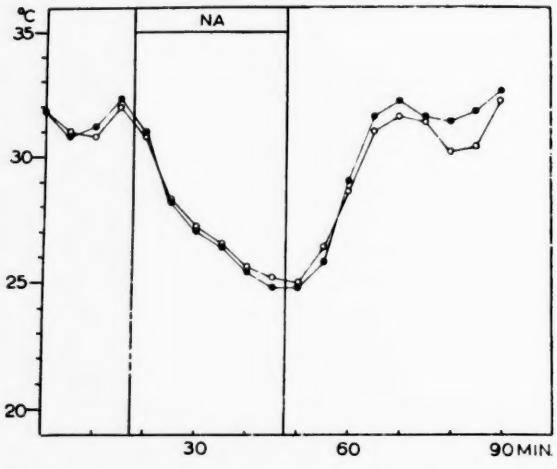

Fig. 4. — The fingertip temperature falls throughout the noradrenaline infusion (0.2 μg/kg/min., for 30 min.) but rises again after its termination as in Fig. 1. The change is quite similar in the corresponding fingers of both hands, Reaction type II.

Case No. 23 (a man of 26). Room temperature 23.5°C.

O—O—O right thumb; ●—●—● left thumb.

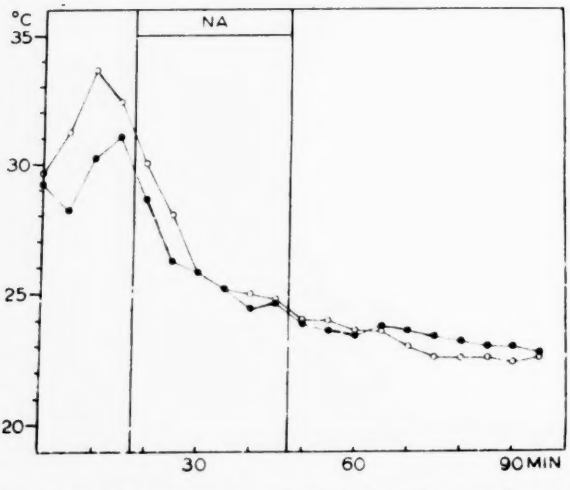

Fig. 5. — The fingertip temperature falls during the noradrenaline infusion (0.2 μg/kg/min., for 30 min.) as in Fig. 4 but does not rise again when the infusions is over: it remains at the low level. Reaction type III.

Case No. 17 (a woman of 30). Room temperature 22.5°C.

O—O—O right thumb; ●—●—● left thumb.

or later, sometimes only after 10—30 minutes had elapsed. If the temperature began to rise in the 3rd phase, it generally rose steeply and considerably. But there were cases in which no temperature rise was registered during the period of observation after the noradrenaline infusion. Fig. 5 shows such a case. Comparing this with Fig. 4, it will be seen that both cases had practically the same initial fingertip temperature and that the temperature drop shows good correspondence. In Fig. 4, however, a temperature rise occurred in the 3rd phase which is absent in Fig. 5. On the other hand, a pronounced temperature increase in the fingertips was established several times after noradrenaline infusion although the initial temperature was low, corresponding to the room temperature throughout the 1st and 2nd phase of the study (Fig. 2).

A general characteristic of the temperature changes was that they followed a fairly parallel course in the corresponding fingers of both hands and in the different fingers of the same hand.

To elucidate the significance of the temperature curves measured from the fingertips in connection with noradrenaline infusion, *mechanically induced ischemia* in one finger was included in the investigation in several cases. This was accomplished by winding a tight rubber band round the finger from tip to base, thus driving the blood out of the finger and preventing fresh arterial blood from flowing into the finger. With the band in situ the finger was pale and no cyanosis occurred, which was evidence of the completeness of the occlusion. The band was usually placed on the little finger of each hand for 30 min., removed from one hand 15 min. prior to the inception of the noradrenaline infusion and from the other after the noradrenaline infusion was half complete, *i.e.* had lasted 15 min. The test subjects tolerated the band well. At the right degree of tightness neither the band nor the ischemia caused any pain in the finger. The aim of this procedure was to obtain a control curve which would simulate the effect of »maximal vasoconstriction» and its sudden release on the finger temperature. The following points were established (Figs. 6—13).

(i) Mechanical occlusion of the blood flow to the finger caused a temperature drop which was sharp initially, evened gradually and in c. 20 min. approached its minimal level; this minimum,

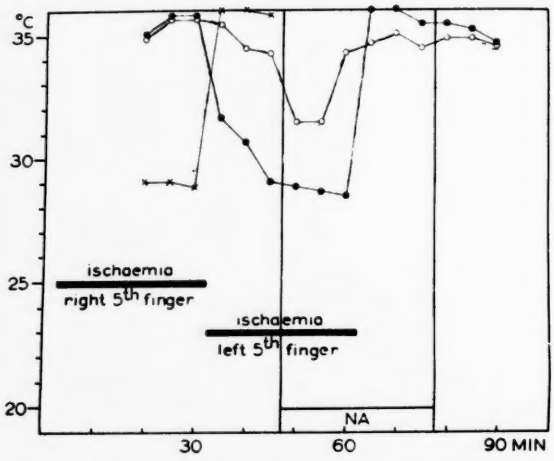

Fig. 6. — A temperature change in agreement with reaction type I in the left thumb during the noradrenaline infusion (0.2 μg/kg/min., for 30 min.); the temperature falls at the beginning of the infusion but rises again in the course of the infusion. The post-ischemic temperature increase in the little fingers is equally great before and during the noradrenaline infusion.

Case No. 38 (a man of 26). Room temperature 23.5 C.

O—O—O left thumb; ●—●—● left little finger; ×—×—× right little finger.

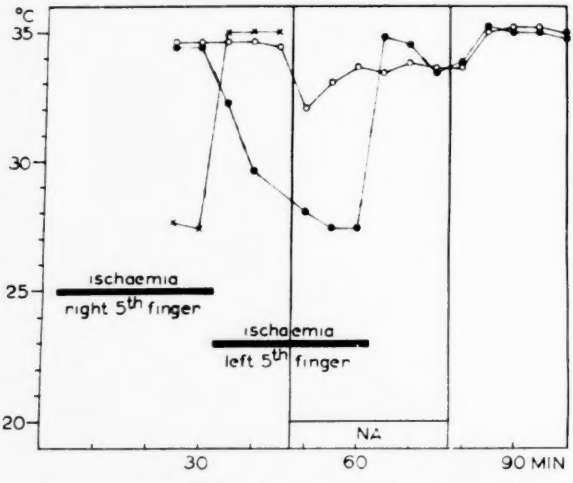

Fig. 7. — The temperature changes in the left thumb are of reaction type I. The post-ischemic temperature increase in the little fingers is equally great before and during the noradrenaline infusion.

Case No. 27 (a man of 34). Room temperature 23.3 C.

O—O—O left thumb; ●—●—● left little finger; ×—×—× right little finger

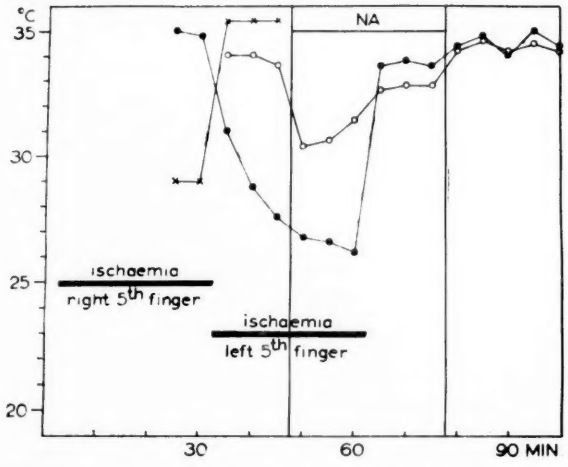

Fig. 8. — The temperature changes in the left thumb are of reaction type I An almost equal post-ischemic temperature increase in the little fingers in connection with reactive hyperemia is registered both before and during the noradrenaline infusion.

Case No. 37 (a man of 31). Room temperature 23.5° C.

O—O—O left thumb; ●—●—● left little finger; ×—×—× right little finger.

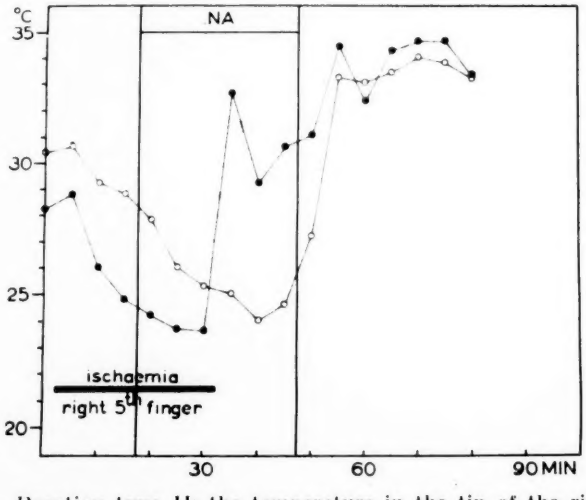

Fig. 9. — Reaction type II: the temperature in the tip of the right thumb falls during the noradrenaline infusion, but it begins to rise sharply immediately after its termination. The graph also shows the post-ischemic temperature increase in the little finger of the right hand during the noradrenaline infusion.

Case No. 34 a (a man of 28). Room temperature 22.7° C.

O—O—O right thumb; ●—●—● right little finger.

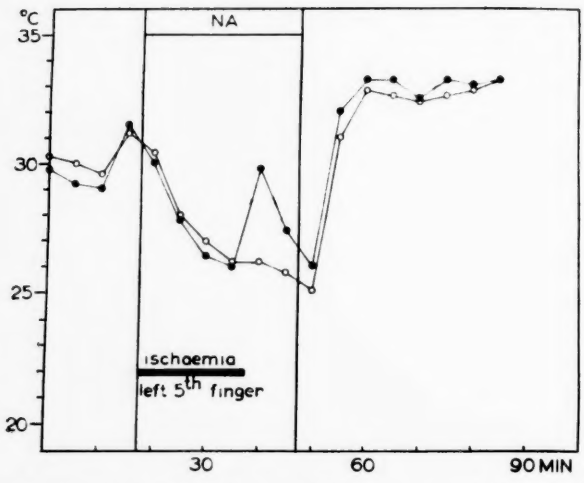

Fig. 10. — Temperature changes of reaction type II in the left thumb. The post-ischemic temperature rise in the little finger of the left hand during the noradrenaline infusion is small compared with the reaction in Fig. 9 and with the spontaneous temperature rise in the thumb and little finger when the infusion is over.

Case No. 42 (man of 23). Room temperature 22.0°C.

O—O—O left thumb; ●—●—● left little finger.

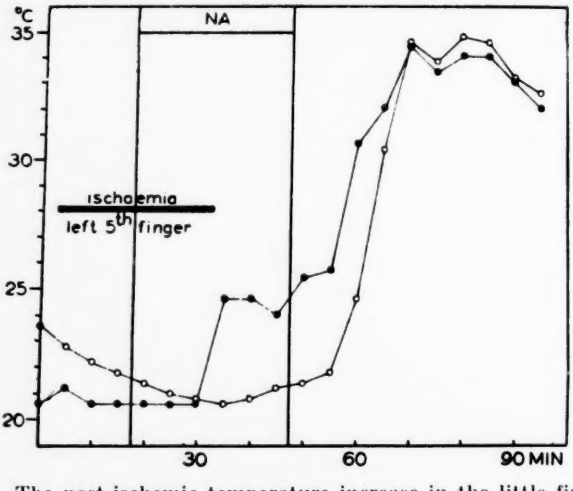

Fig. 11. — The post-ischemic temperature increase in the little finger of the left hand during the noradrenaline infusion is fairly small. A sharp temperature rise is registered in the thumb and little finger 10 min. after the termination of the noradrenaline infusion: reaction type II.

Case No. 32 (a man of 20). Room temperature 22.0°C.

O—O—O left thumb; ●—●—● left little finger.

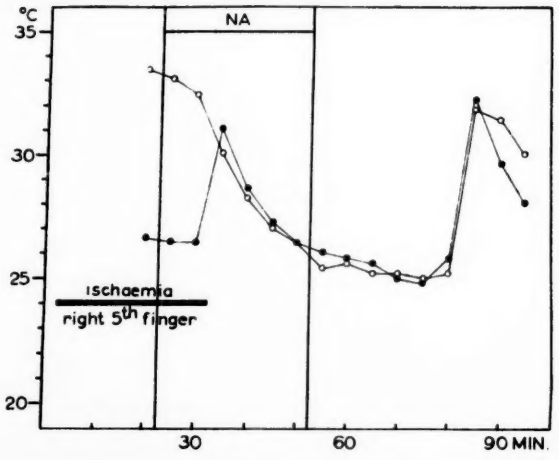

Fig. 12. — The temperature falls in the left thumb during the noradrenaline infusion. There is a sudden and sharp temperature increase in the fingertips 30 min. after the termination of the noradrenaline infusion. The post-ischemic temperature increase during the noradrenaline infusion is measured in the little finger of the right hand. Reaction type II.

Case No. 6 (a woman of 23). Room temperature 23.0°C.

O—O—O left thumb; ●—●—● right little finger.

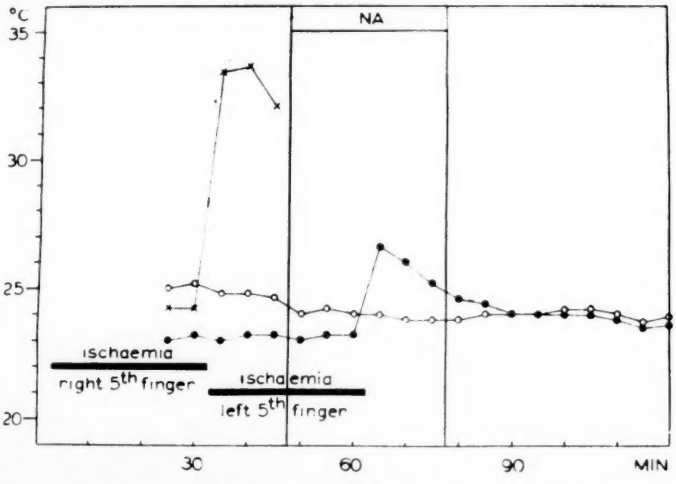

Fig. 13. — The already initially low temperature in the left thumb does not change noticeably during the noradrenaline infusion and no temperature rise follows it: reaction type III. The post-ischemic temperature rise in the little finger of the right hand before the infusion is high whereas the comparable reaction in the little finger of the left hand during the noradrenaline infusion is fairly small.

Case No. 20 (a woman of 29). Room temperature 23.5°C.

O—O—O left thumb; ●—●—● left little finger; ×—×—× right little finger.

which depended on the starting temperature and the effect of the temperature of the hand and the other fingers, was around 24—27°C. The temperature rise following the removal of the ring was rapid, reaching its maximum in 5 min. Reactive hyperemia naturally played a part in this sharp temperature increase. The maximal values in connection with reactive hyperemia approximate 35—36°C. A temperature of 36.0°C was registered only once (Fig. 6). When the initial temperature was very low, occlusion of the blood flow did not lower the temperature (Fig. 11). But even then the temperature increase due to reactive hyperemia was high (Fig. 13).

(ii) The temperature decreases influenced by the noradrenaline infusion were markedly similar to the control curves in shape and reached roughly the same minimal level unless the fall was interrupted during the course of the noradrenaline infusion. The spontaneous temperature increase that followed noradrenaline infusion sometimes reached its maximum in 5 min. Generally it was slower, but usually reached the maximum within 15 min.

This test arrangement also made it possible to compare the temperature increase due to reactive hyperemia before and during noradrenaline infusion. The following observations were made (Figs. 6—13).

(i) The temperature rise in connection with reactive hyperemia during noradrenaline infusion was very pronounced in the cases in which the noradrenaline-induced fall in temperature ceased and was reversed before the end of the infusion (Figs. 6—8).

(ii) The temperature increase caused by reactive hyperemia during noradrenaline infusion was retarded in varying degrees in the cases in which the fingertip temperature fell throughout the noradrenaline infusion but rose spontaneously after its termination (Figs. 9—12).

(iii) The temperature increase in connection with reactive hyperemia during noradrenaline infusion was even more markedly inhibited in the cases in which no spontaneous rise occurred after the noradrenaline infusion than in the cases of the preceding group (Fig. 13).

The temperature rise caused by reactive hyperemia during noradrenaline infusion was studied in 27 cases. Nine of them belonged to the first of the three groups listed above, 12 to the second and 6 to the third. Fig. 14 shows the means for each

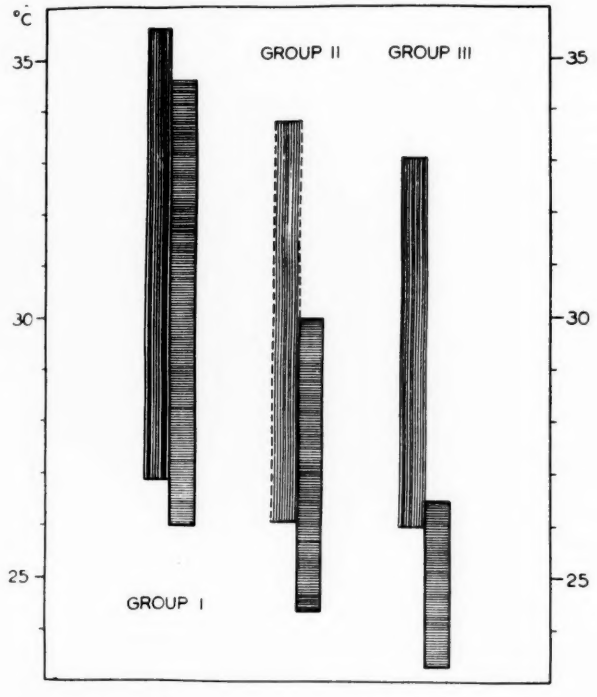

Fig. 14. — Post-ischemic temperature increase in the fingers before and during the noradrenaline infusion in the form of mean values. Each reaction type is treated separately. The first column represents in each group the mean temperature increase before the noradrenaline infusion and the second column the change during the infusion. The column representing the post-ischemic temperature increase in group II before the noradrenaline infusion is the mean of the total measurements available (see the text).

group seperately. Of each pair of colums, the first is the control column illustrating the mean temperature increase in connection with reactive hyperemia before the noradrenaline infusion, and the second one presents the mean rise during the infusion. The bottom end of each column indicates the temperature mean just before removal of the rubber band and the top end the temperature mean 5 min. after the removal of the band when the increase due to reactive hyperemia is at its maximum. The control mean was

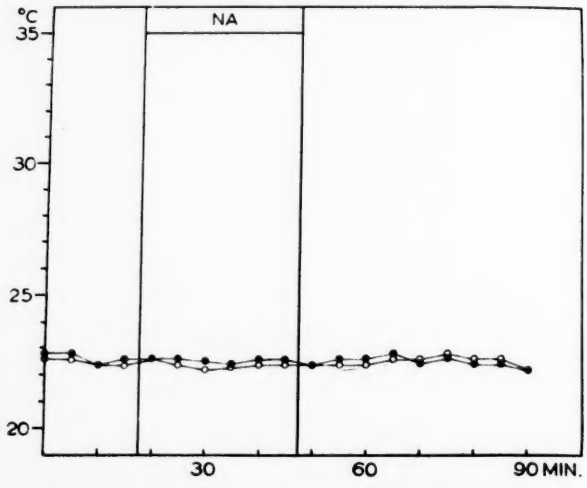

Fig. 15. — No changes occur in the toetip temperature during the examination. The result is the same in the majority of the cases.

Case No. 5 a (a woman of 22, cf. Fig. 2). Room temperature 23.0°C.

O—O—O right big toe; ●—●—● left big toe.

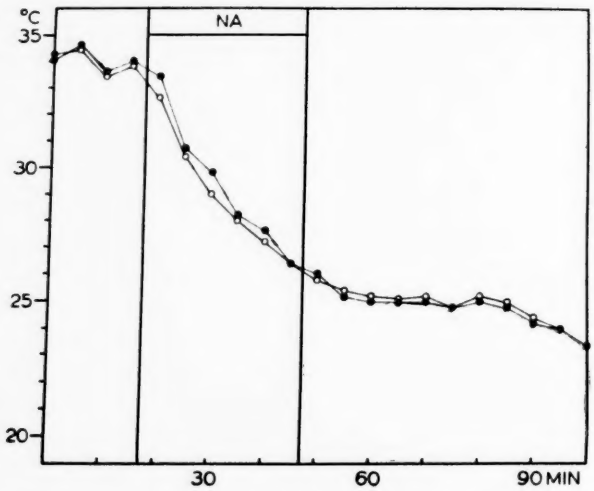

Fig. 16. — The toe temperature falls during the noradrenaline infusion and then remains constant at the low level.

Case No. 11 b (a woman of 21). Room temperature 22.0°C.

O—O—O right big toe; ●—●—● left big toe.

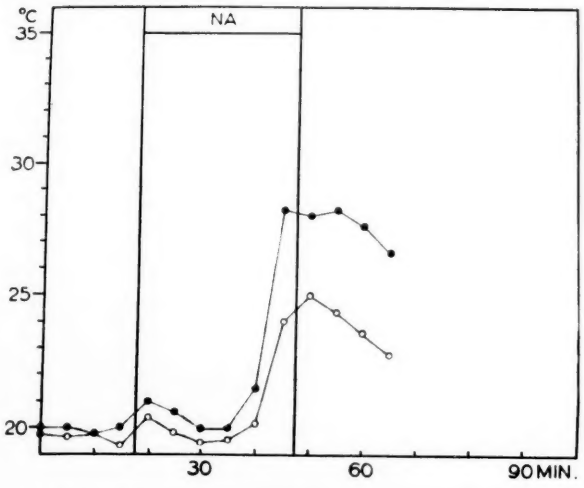

Fig. 17. — A distinct increase occurs in the toetips towards the end of the noradrenaline infusion.

Case No. 36 (a man of 22, cf. Fig. 3). Room temperature 22.6°C.

O—O—O right big toe; ●—●—● left big toe.

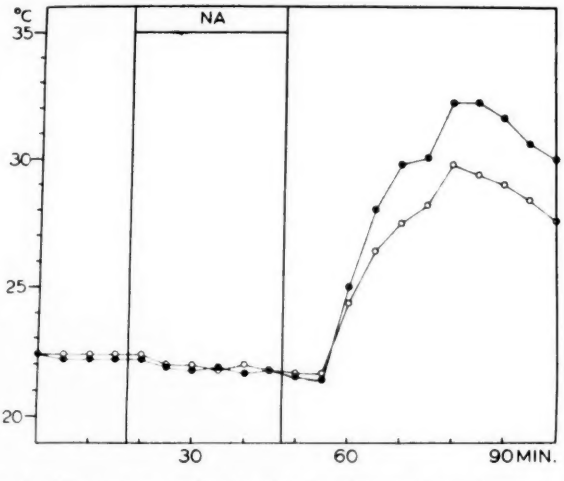

Fig. 18. — A vigorous warming begins in the toetips 10 min. after the termination of the noradrenaline infusion.

Case No. 16 (a woman of 20, cf. Fig. 21). Room temperature 22.5°C.

O—O—O right big toe; ●—●—● left big toe.

obtained from 6 examinations in the first group and in the third group. In the second group the temperature rise caused by reactive hyperemia was measured before noradrenaline infusion in 2 cases only. Therefore the mean of all the 14 cases was entered as the control column in this group. The figure shows that the temperature climb caused by reactive hyperemia during noradrenaline infusion was inhibited least in the first group and most in the third group.

TOES

Compared with the findings concerning fingertip temperatures, temperature changes in the toetips were very slight. Thermometry was performed on 25 persons (13 men and 12 women) of the normal series in connection with a total of 31 noradrenaline infusions. The results obtained were in the main as shown in Fig. 15. The toe temperature was at its minimum before the beginning of the noradrenaline infusion and could not be influenced by the noradrenaline. The temperature kept at the same low level after the termination of the noradrenaline infusion. In the few cases in which toe temperature was higher it dropped during noradrenaline infusion and then remained at the lower level (Fig. 16).

Temperature changes diverging from this general scheme were established in 2 cases only. Fig. 17 presents one of these in which the low toe temperature began to rise in the middle of the noradrenaline infusion; it actually rose fairly high but fell again after the termination of the noradrenaline infusion without any subsequent rise. The finger temperature also began to rise in this subject towards the end of the noradrenaline infusion (Fig. 3). In the other case introduced in Fig. 18, the toe temperature began to rise sharply c. 10 min. after the termination of the noradrenaline infusion. A similar thermal reaction occurred also in the fingers of the same individual.

WRISTS AND ANKLES

The temperature changes in the skin of the wrist in connection with noradrenaline infusion were similar in principle to those established in the tips of the fingers. The changes in the wrists, however, were quantitatively smaller than those in the fingers. A

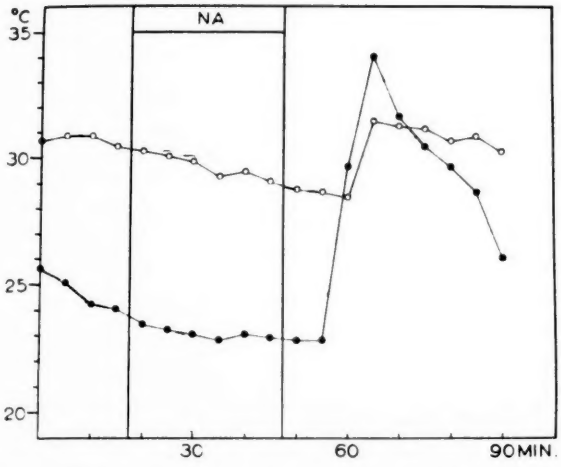

Fig. 19. — Temperature changes in the skin of the wrist and in the tip of the little finger of the same hand. There is a vigorous warming in the fingertip after the noradrenaline infusion: reaction type II. A similar, though smaller temperature change is established in the wrist, beginning a little later.

Case No. 5 a (a woman of 22). Room temperature 23.0°C.

O—O—O right wrist; ●—●—● right little finger.

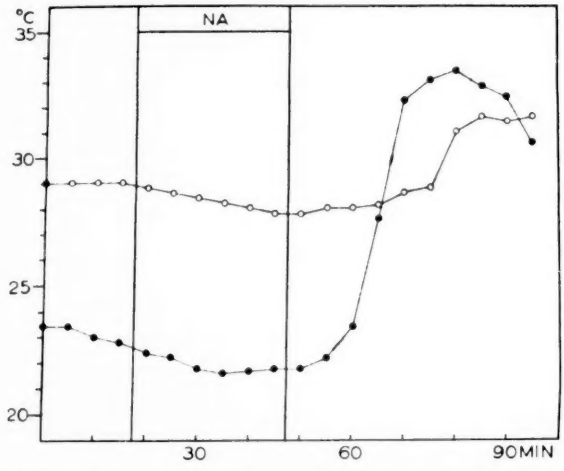

Fig. 20. — A temperature increase in the skin of the wrist follows slightly later the temperature increase in the fingertips after the noradrenaline infusion. The temperature change in the fingertip represents reaction type II.

Case No. 32 (a man of 20). Room temperature 22.0°C.

O—O—O right wrist; ●—●—● right thumb.

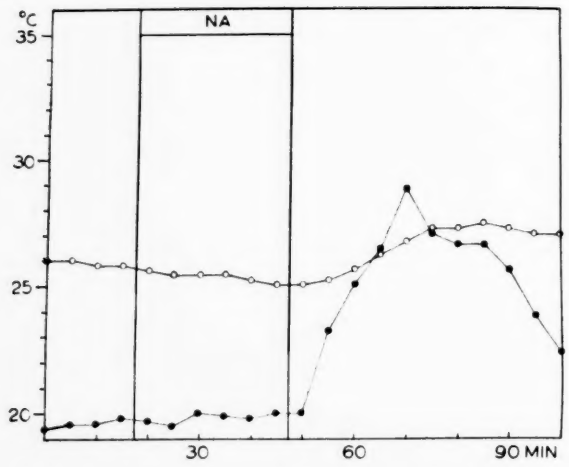

Fig. 21. — A temperature increase following the termination of the noradrenaline infusion in the wrist and in the fingertip (reaction type II).

Case No. 16 (a woman of 20). Room temperature 22.5°C.

O—O—O right wrist; ●—●—● right little finger.

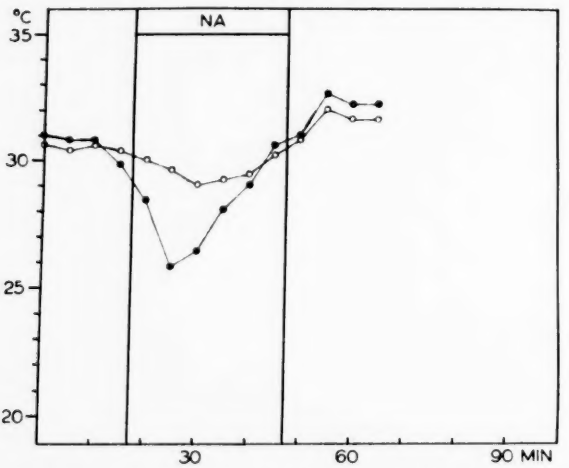

Fig. 22. — The temperature changes in the fingertip during the noradrenaline infusion correspond to reaction type I. The temperature rises slightly also in the skin of the wrist during the latter half of the noradrenaline infusion.

Case No. 36 (a man of 22). Room temperature 22.6°C.

O—O—O left wrist; ●—●—● left little finger.

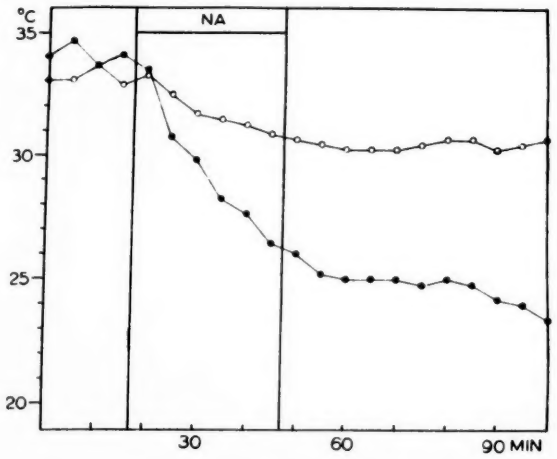

Fig. 23. — The temperature of the skin of the ankle and of the tip of the toe fall during the noradrenaline infusion. There is no thermal reaction after the noradrenaline infusion.

Case No. 11 b (a woman of 21). Room temperature 22.0°C.

O—O—O left ankle; ●—●—● left big toe.

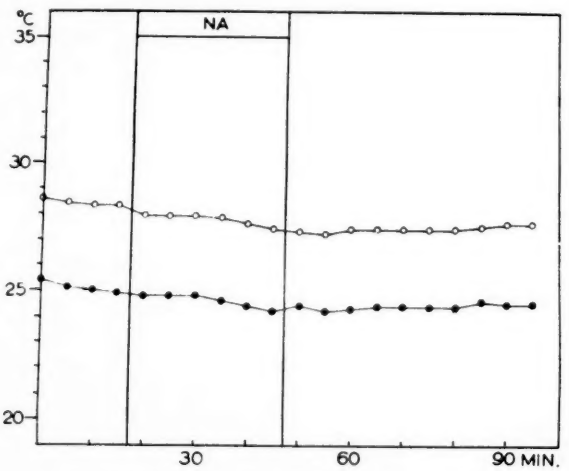

Fig. 24. — A small temperature fall in the skin of the ankle during the noradrenaline infusion.

Case No. 15 (a woman of 59). Room temperature 23.2°C.

O—O—O left ankle; ●—●—● left big toe.

slight temperature fall generally occurred during the course of the noradrenaline infusion. If the finger temperature began to rise in the middle of the noradrenaline infusion a similar change occurred in the skin of the wrist (Fig. 22). If the finger temperature rose after the noradrenaline infusion, the wrist temperature responded similarly (Figs. 19—21). In the cases showing no increase in finger temperature following the noradrenaline infusion the wrist temperature also stayed at the level established at the end of the infusion. A general feature was that the temperature rise in the wrist during or after the noradrenaline infusion began a little later than that in the fingers. This can be seen in Figs. 19—22.

The temperature changes demonstrated in the skin of the medial surface of the ankle were even smaller, but they were similar in character to those in the skin of the wrist. If the toe temperature was very low when the noradrenaline infusion was started that of the skin of the ankle was also fairly low and no temperature changes were registered during the examination. If, on the other hand, the temperature of the toes and the ankle was higher at the start, the temperature in the skin of the ankle fell by 2—3°C during the infusion. The ankle temperature always remained at the level it reached at the end of the noradrenaline infusion and no temperature increase was established in the skin of the ankle even in the 2 cases in which the toe temperature rose in the final phase and after the noradrenaline infusion. Figs. 23 and 24 give examples of characteristic temperature changes in the skin of the ankle.

PROXIMAL PARTS OF THE LIMBS

Thermometry performed on the proximal parts of the limbs in connection with noradrenaline infusion showed temperature changes entirely different from those in the distal parts of the limbs. *There were sharp temperature rises in the forearms, legs and thighs during the noradrenaline infusion in many cases.* These temperature elevation reactions varied considerably in intensity and were not regular in their occurrence. The temperature could also remain unchanged throughout the examination. No distinct temperature drop was established at the proximal measuring points during the noradrenaline infusion. The typical temperature rise began immediately after the beginning of the infusion. The tem-

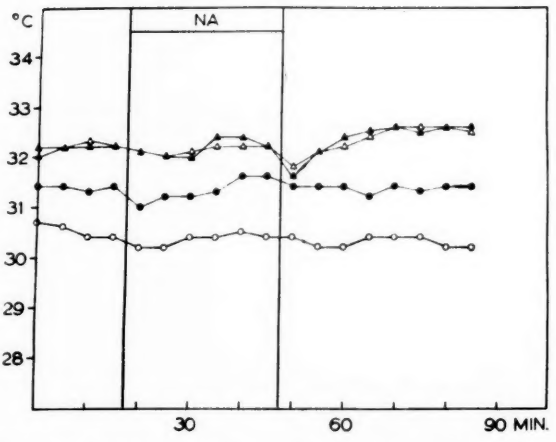

Fig. 25. — This case shows no distinct temperature changes in the skin of the forearms and thighs in connection with the noradrenaline infusion.

Case No. 42 (a man of 23). Room temperature 22.0°C.

O—O—O right forearm; ●—●—● left forearm;
△—△—△ right thigh; ▲—▲—▲ left thigh.

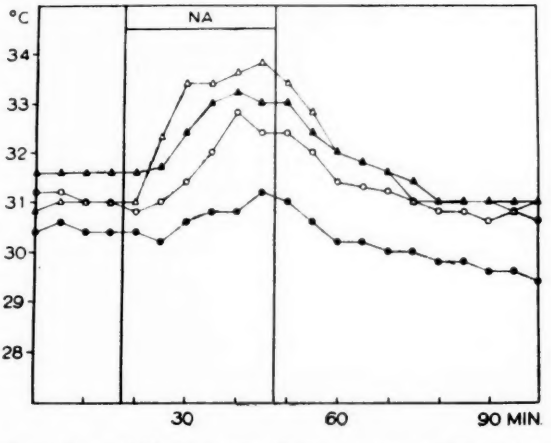

Fig. 26. — There is a distinct temperature increase in the skin of both legs and the right forearm during the noradrenaline infusion. The temperature increase is smaller in the left forearm. The changes return to the initial values after the infusion is over.

Case No. 11 b (a woman of 21). Room temperature 22.0°C.

O—O—O right forearm; ●—●—● left forearm
△—△—△ right leg; ▲—▲—▲ left leg.

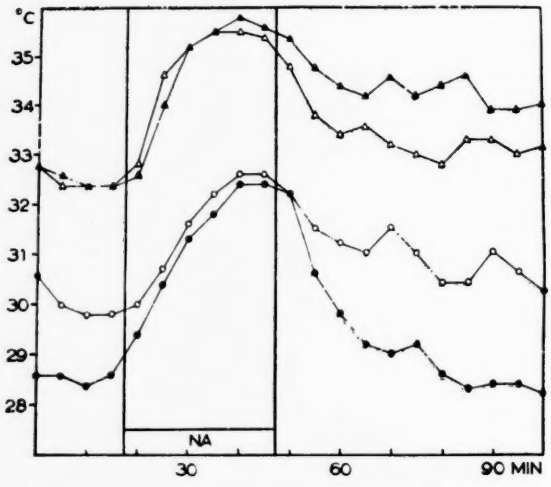

Fig. 27. — A vigorous temperature increase in the skin of the forearms and thighs during the noradrenaline infusion.

Case No. 12 (a woman of 19). Room temperature 22.3°C.

O—O—O right forearm; ●—●—● left forearm;
△—△—△ right thigh; ▲—▲—▲ left thigh.

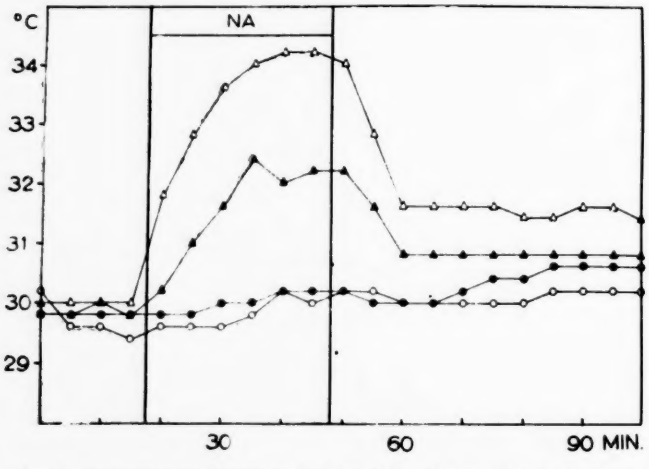

Fig. 28. — A temperature increase in the skin of the thighs during the noradrenaline infusion. No distinct changes are established in the skin temperature of the forearms.

Case No. 4 (a woman of 21). Room temperature 22.5°C.

O—O—O right forearm; ●—●—● left forearm;
△—△—△ right thigh; ▲—▲—▲ left thigh.

TABLE 1

Skin temperature changes in limbs at the proximal measuring points in *women* of the normal series.

Case No.	Forearms		Legs		Thighs		Feeling of warming
	Right	Left	Right	Left	Right	Left	
1 a	++	+++	+—	++			+
1 b	—	—	—	—	++	++	
2	—	—	+	++			—
3 a	—	—	—	—			—
3 b	—	—	—	+—	—	—	—
4	—	—	+—	++	+++	+	—
5 a	—	+	++	++	++	+	+
5 b	+	+++	++	+++	++	+++	+
6	—	—					—
7	+—	+—					—
8	+	++					+
9 a	++	—	++	+	+	++	+
9 b	++	+	+	+	+	++	+
10	+	—					—
11 a	++	+—	—	—			+
11 b	+	+	++	+	+	+	
12	++	++	+	++	++	++	—
13	+	+					+
14	+—	+					—
15	+	+	++	+++	+	+++	
16	+—	+	+	+	+	++	—
17	—	+					+
18	+	+—					+
19	+—	+++					—
20	—	+—					+
21	+	+++	—	++	+—	++	+

The temperature increases during the noradrenaline infusion were classified by the intensity of the change into positive reactions of different degrees as follows:

0.5—0.9° : +—
1.0—2.4° : +
2.5—3.9° : ++
4.0— : +++

The subjective feeling of warming in the limbs in the beginning of the noradrenaline infusion reported by the individual is entered in the table as +.

perature first rose sharply and then gradually approached its maximum at the end of the infusion. It began to fall immediately the infusion ceased and returned gradually to the former level or slightly above it. Figs. 25—28 show some typical examples.

TABLE 2

Skin temperature changes in limbs at the proximal measuring points in *men* of the normal series

Case No.	Forearms		Legs		Thighs		Feeling of warming
	Right	Left	Right	Left	Right	Left	
22	—	—	+	—	+	+	+
23	—	+	—	+	++	+	—
24 a	—	—					—
24 b	—	—					—
25	—	—	+—	—	+—	—	—
26	—	+—	—	+	++	+	+
27	—	—					—
28	—	—	—	—	+—	—	—
29 a	—	—					—
29 b	—	+					—
30	—	+—					—
31	—	—	—	—			—
32	—	+—	—	—	—	—	—
33 a	—	—					—
33 b	—	—					—
33 c	—	—					—
34 a	—	—	—		—		—
34 b	—	—	—		+—		—
35	—	—					—
36	—	—	—	—	—	—	—
37	—	+—					—
38	—	—					—
39	+	+—	+	+	++	+	—
40	—	—					—
41	—	—	—	—	—	—	—
42	—	—	—	—	—	—	—
43	+—	+	—	—	+—	++	—
44	—	—	—	—	++	++	—

The same method of recording as in Table 1.

Tables 1 and 2 give the temperature changes in the proximal parts of the limbs in the normal series separately for men and women. It appears from the tables that the increase in temperature which occurred during noradrenaline infusion varied considerably in intensity at different sites. It did not always occur, even in the same individual, at all the measuring points, not even in symmetrical parts of the extremities. Re-examinations also failed to

give identical results with those obtained earlier for the same individuals. It could not be established that the site of infusion had any significance for the occurrence of the temperature rise reaction.

Mean value curves of the skin temperature changes in the proximal parts of the limbs were plotted separately for men and women. They are shown in Figs. 29 and 30. The means were determined from the normal series. The mean curve for the forearm of women was calculated from 52 temperature curves, for the leg from 32 and for the thigh from 24 temperature curves. For the men the mean value curves were calculated correspondingly from 56, 28 and 26 temperature curves.

A prominent feature in Tables 1 and 2 and Figs. 29 and 30 is *the greater frequency and intensity of the temperature rise reaction in women than in men.* In only 1 of the 21 women examined was no temperature increase established during the noradrenaline infusion, and in fact only the temperature changes in the forearms were studied in this case. There was also a woman in whom no temperature increase was registered in the forearms and legs at the first examination but who showed in the re-examination a slight rise in one leg. Only 13 of the 23 men examined showed a temperature increase, and it is worth noting that their reactions were generally weaker than those in the women.

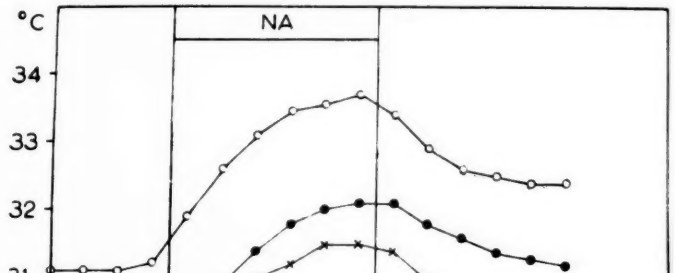

Fig. 29. — Temperature changes in the skin of the proximal parts of the limbs during the noradrenaline infusion, means for the *female* group.

O—O—O thighs; ●—●—● legs; ×—×—× forearms.

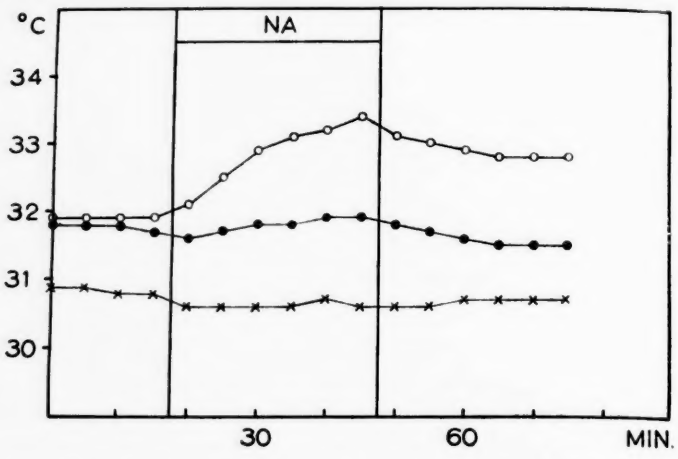

Fig. 30. — Mean temperature changes in the proximal parts of the limbs *in men* in connection with the noradrenaline infusion.

O—O—O thighs; ●—●—● legs; ×—×—× forearms.

As regards site, a temperature increase during noradrenaline infusion seemed to be *commonest in the thighs and least frequent in the forearms* in both men and women.

The temperature increases in the proximal parts of the limbs sometimes seemed to be associated, especially in women, with a subjective feeling of warmth. It was mostly localised in the elbows and knees, more rarely in the legs and thighs. Tables 1 and 2 have an annotation as to whether or not the test subject reported this sensation of warmth.

CONTROLS

The control study in which physiological saline solution alone was infused was made on six subjects. Skin thermometry was performed only on the upper limbs.

In cases 30 and 37 the fingertip temperature remained at 33—34°C throughout the examination. No changes occurred in the fingertip temperatures after changing the infusion fluids. Cases 22 and 32 showed spontaneous variation in the fingertip temperatures which was not connected with the changing of the infusion fluids. The temperature varied from 21° to 23° in case 22 and between 27° and 32°C in case 32. The finger temperatures remained evenly low at 21—22°C in cases 18 and 28.

In the noradrenaline infusion study, the fingertip temperature fell in the initial phase of the infusion in cases 30 and 37 but rose again as the infusion progressed. In cases 22, 28 and 32 the finger temperature either dropped or was low throughout the noradrenaline infusion but the termination of the infusion was followed by a sharp temperature increase. The fingertip temperature was consistently low throughout the noradrenaline infusion study in case 18.

The temperature increaces caused by reactive hyperemia were measured in the little finger of each hand at intervals of 30 min. in the control study. The temperature increases were of the same magnitude in both fingers in all the cases. Reactive hyperemia in the little finger did not affect the thumb temperature of the same hand.

No temperature changes were established in the wrists and forearms during the control studies except for an even, slight temperature drop in some cases.

OTHER OBSERVATIONS

Blood Pressure. — The blood pressure was measured before the noradrenaline infusion, after 25 min. of infusion and 30—45 min. after the infusion had been completed. Noradrenaline distinctly raised both the systolic and the diastolic pressure. The mean blood pressures for the whole normal series were 114/76—144/91—114/74. The respective means for the women were 113/75—140/90—113/73 and for the men 115/78—147/92—116/75. (Tables 7 and 8).

Heart Rate. — The heart rate slowed down under the influence of the noradrenaline infusion; it remained fairly constant during the infusion, rose rapidly above its initial level after termination of the infusion and then returned gradually to its former level. The mean of several pulse rates was adopted as the heart rate following the noradrenaline infusion. The means before, during and after the noradrenaline infusion were 64—53—70 per minute and, separately, for women 68—56—74 and for men 61—50—66. (Tables 7 and 8.)

Colour of the Skin. — Loss of colour in the face and more or less distinct pallor in the hands were observed at the start of the noradrenaline infusion. This pallor persisted throughout the in-

fusion. A striking feature was that distinct pallor persisted in many cases to the end of the infusion in the hands and fingers although the finger temperature had risen during the noradrenaline infusion even above the initial values. A typical flushing of the face was established after the termination of the infusion, and associated with it a subjective feeling of warmth in the face. The flushing varied considerably in intensity in the different cases and in some cases was not demonstrable at all. Smarting of the eyes and a flow of tears accompanied the flushing of the face in 2 cases. The flushing always occurred a couple of minutes after the end of the noradrenaline infusion. No corresponding flushing was observed in any of the cases in the hands, their colour was restored gradually, almost unnoticeably.

Subjective Sensations. — The subjective feelings during the noradrenaline infusion were mild and never necessitated a reduction of the dosage. Many of the subjects reported no sensations at all. The commonest symptoms were a feeling of weight or compression in the chest under the sternum which occurred immediately the infusion was started, and slight difficulty in breathing. These symptoms generally passed off in a few minutes. A fairly common sensation also was limpness and a feeling of muscular weakness in the lower limbs, especially in the knee region, which was felt for some time in the initial phase of the infusion. Slight headache occurred 5 times in the 55 examinations of the normal series. The headache was of short duration in 2 cases and passed off in the course of the infusion. However, it lasted for the duration of the infusion in 3 cases and afflicted the subject for several hours after the examination in 2 cases. Mention was made of the subjective feeling of warmth in the knee and elbow regions. This sensation was generally manifested as a wave of heat in the initial stage of the noradrenaline infusion and it passed off after a short time.

In one case (No. 14), when the noradrenaline infusion had continued for 10—15 min., the subject reported a sensation of pressure at the jugulum, as if a collar were constricting the neck. This sensation was aggravated further and it was finally found that the base of the neck had swelled. The swelling was found to be due to the thyroid gland for after the experiment it could be recognised by palpation that the distinctly visible eminence was diffusely enlarged thyroid which was soft in consistency and not tender.

The swelling at the base of the neck was still demonstrable in the evening of the same day 7 hours after the test. However, on the following day the person was subjectively symptom-free and palpation revealed that the thyroid was normal in size. Laboratory examinations two months later gave the following findings: the protein-bound iodine of the serum was 6.0 γ-% and serum cholesterol 279 mg-%. Barnett *et al.* (21) reported a similar soft swelling in the thyroid gland in 2 healthy subjects during noradrenaline infusion of 30 μg per minute for 16 and 40 minutes.

Some of the subjects also showed other symptoms which occurred towards the end of the noradrenaline infusion. In 2 cases (24 b and 40) the subjects became very drowsy towards the end of the infusion and considerable effort was required to keep them awake by engaging them in non-stop conversation. Immediately after the noradrenaline infusion was over both subjects picked up and the drowsiness disappeared completely in c. 10 min. With 2 subjects (34 and 40) the speech became sluggish and thick in the final phase of the noradrenaline infusion and they found it difficult to pronounce some words. This too passed off rapidly after the termination of the noradrenaline infusion.

COMMENTS

Judging by the results achieved, intravenous noradrenaline infusion at a rate of 0.2 μg/kg/min. causes vasoconstriction in the fingers. This vasoconstriction is manifested as a temperature decrease and seen against the control curves produced by mechanical occlusion of the circulation it must be regarded as quite marked. In the cases in which the finger temperature was close to room temperature and could not fall during the noradrenaline infusion, the increasing effect on vasoconstriction of the infusion was seen as a weakening of the temperature increase caused by reactive hyperemia. There were cases, however, in which the temperature increase in the fingertips was interrupted and the temperature began to rise again in spite of continuing noradrenaline infusion. The temperature rise increased further in these cases after the termination of the noradrenaline infusion. In many cases in which the temperature dropped throughout the process of noradrenaline infusion there likewise occurred a very sharp temperature increase after its termination. This development was sometimes seen

even in cases in which the finger temperature was low prior to starting the infusion. It consequently seems that *the immediate effect of the noradrenaline infusion on the blood vessels in the fingertips is vasoconstriction, but that when the intravenous infusion continues forces which are antagonistic to this vasoconstrictive influence are mobilised in the body.* These forces may gain predominance in spite of the continuous effect of the noradrenaline or emerge only after the termination of the noradrenaline infusion.

This view is supported by the results obtained in the following experimental arrangement (Fig. 31). The rate of drip of the

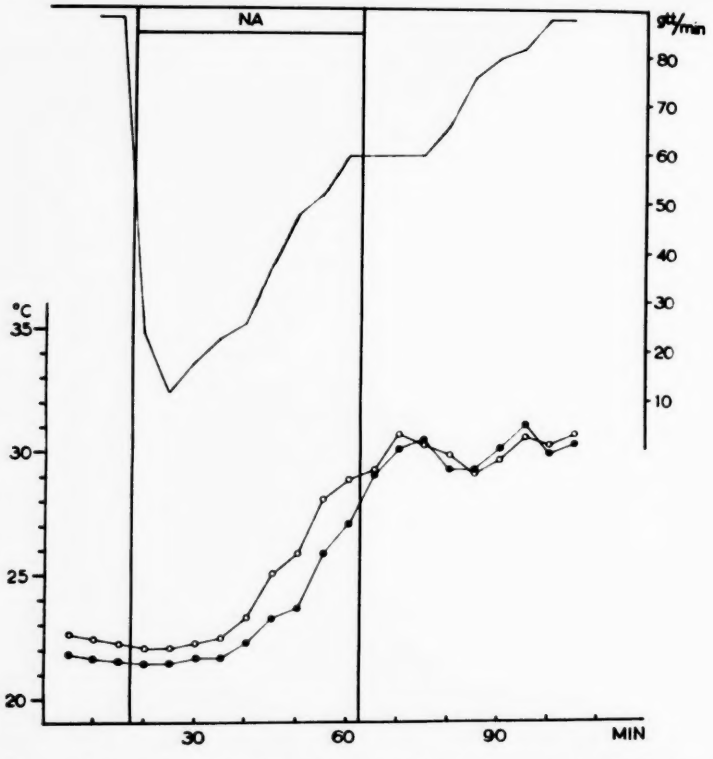

Fig. 31. — A test in which the drip rate of the noradrenaline solution was allowed to change spontaneously in accordance with the venous vasoconstriction. The 88 drops/min. rate corresponds to a dosage of 0.2 μg/kg/min. The graph shows the changes in the drip rate and the variations in the temperature of the little finger of both hands. The fingertip temperature begins to rise during the noradrenaline infusion once the drip rate has started to rise again spontaneously.

Case No. 24 a (a man of 54). Room temperature 20.0°C.

O—O—O right little finger; ●—●—● left little finger.

physiological saline solution was 88 drops per min. in the first phase of this investigation. In its second phase the noradrenaline infusion began at the same rate but soon slowed down, obviously in consequence of venous constriction and reached its minimum, 12 drops per min., in 5—10 min. The drip rate was not adjusted but plotted on the graph at 5 min. intervals with the temperature measurements. The fingertip temperature was low at the beginning of the investigation and did not fall after the noradrenaline infusion was started. It was, however, observed that when the venous pressure began to decrease spontaneously and the rate of infusion speeded up again, the fingertip temperatures began concurrently to rise. The noradrenaline infusion lasted exceptionally 45 min. At the end of the infusion the drip rate had increased to 60 drops per min. and the temperature of the finger tips rose to 30°C. Exactly the same reaction was obtained a couple of days later in a control study of the same person and later also in another subject examined in the same way (Case 35). The gradual release of the noradrenaline-induced intense initial venous constriction and the concomitant increase in the finger temperature in the course of the noradrenaline infusion reflect the effect of the compensatory forces generated by the intravenous infusion of noradrenaline in the body.

The foregoing means that noradrenaline administered intravenously diminishes reflectorily the sympathetic vasomotor tonus and the vasodilator effect resulting from this must be resistant to the direct vasoconstrictor effect of the continuing noradrenaline infusion. Fig. 32 shows an experiment in which the sympathetic tonus in one hand is eliminated by means of stellate block during the noradrenaline infusion. The temperature of the tip of the thumb in this hand rose immediately after the stellate block, whereas a typical spontaneous temperature rise occurred in the other hand after the termination of the noradrenaline infusion. Hence the vasodilatation caused by blocking the sympathetic nerves was resistant to the vasoconstrictor effect of the noradrenaline infusion, at least in the reaction type represented by the person in question.

If it is assumed that the ability of the finger circulation to vary extensively the volume of circulating blood depends decisively on the existence and function of *arteriovenous shunts* it can be concluded that arteriovenous shunts have also a notable role in the thermal reactions established in the investigations under

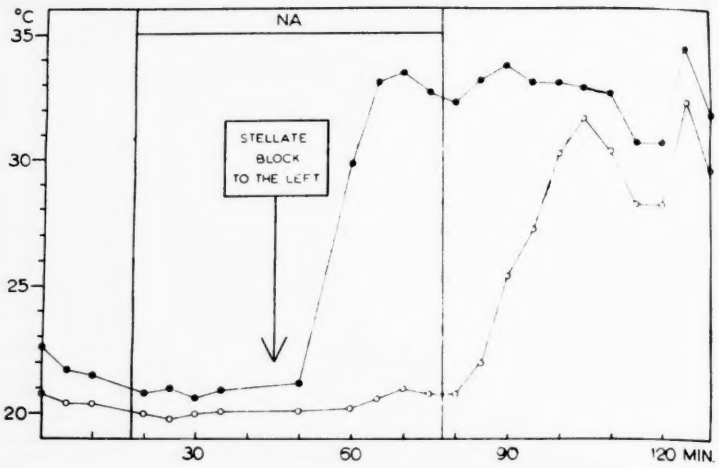

Fig. 32. — Stellate block on the left side during the noradrenaline infusion. It causes a sharp increase in temperature in the fingertips of the left hand while the infusion is in progress. A similar, though slightly weaker and slower rise occurs spontaneously in the fingers of the right hand after the termination of the infusion.

Case No. 7 (a woman of 22). Room temperature 21.5°C.

O—O—O right thumb; ●—●—● left thumb.

review. Vanggaard (165) regarded the large temperature increases in the fingertips provoked by indirect warming and direct cooling as always being evidence of the opening of the arteriovenous shunts. Obviously, then, a warrantable hypothesis is that pronounced temperature rises after noradrenaline infusion reflect the rapid revival of the blood flow through the arteriovenous shunts. In the cases in which the temperature begins to rise during noradrenaline infusion after an initial drop, noradrenaline in the concentration used is not strong enough to maintain the state of constriction in the arteriovenous shunts and they open during the infusion. Even if the vasoconstrictive effect of noradrenaline does not always persist to the end of the infusion in arteriovenous shunts, it could persist in the other parts of the vascular bed of the finger. The *capillaries* obviously respond with vasoconstriction to the noradrenaline infusion throughout its duration as persistent pallor of the fingers to the end of the noradrenaline infusion was also noted in cases in which the finger temperature began to rise during the infusion.

The effect of noradrenaline infusion on the toe temperature was

similar in principle to that on the finger temperature. The toes like the fingers have numerous arteriovenous shunts, and the circulation in the toes is also highly dependent on the central control exerted via the sympathetic vasoconstrictive fibres. However, in normal conditions the toes have a considerably stronger vasomotor tonus than the fingers and this influences the results obtained for the toes. The temperature of the toes was usually low even before the noradrenaline infusion. When this was not the case the temperature dropped during the noradrenaline infusion and remained subsequently low in nearly all the cases. The vasodilator reactions common in the fingers were demonstrated in 2 cases only. They were of the same type as the temperature increases in the fingers.

The temperature changes in the wrists and ankles have followed the changes in the temperatures of the fingers and toes. The wrist and ankle temperatures generally decreased during the noradrenaline infusion. When the infusion was followed by a sharp increase in the finger temperature the wrist temperature also rose, though to a smaller extent. It seems probable that the wrist temperature changes are largely only reflections of the changes in the circulation in the fingers which are transmitted by the blood returning from the fingers via the superficial veins, as was suggested by Grant and Pearson (88). The wrists and the ankles in any case form an intermediary tract between the most distal and proximal parts of the limbs in which entirely contrary temperature changes were established during the noradrenaline infusion.

No distinct temperature drop in connection with noradrenaline infusion was ever established in the forearms, thighs and legs. Conversely, sharp temperature rises were demonstrated; they were characterised by asymmetry and by a certain inconstancy in regard to site of occurrence and intensity. The reaction was more pronounced in women than in men. The character of the reaction is considered in more detail in the discussion.

VARIATION TYPES IN TEMPERATURE REACTIONS OF FINGERS

The temperature curves obtained from the fingertips in connection with intravenous noradrenaline infusion differed notably in different individuals. It seems evident that there are individually varying factors modifying the effects of noradrenaline and the

reaction produced in the organism by the intravenously infused noradrenaline which has a counteractive influence on the direct vasoconstrictive effect of noradrenaline. The finger temperature in each phase of the study is dependent on the quantitative relations between these opposite forces. An additional factor associated with them is the vasomotor state existing in the vessels of the finger in the test conditions. The investigations were made in hypothermal conditions with the result that a more or less pronounced vasoconstriction, dependent on individual factors, prevailed in the fingers before the noradrenaline infusion was started. The vasoconstrictive effect of the noradrenaline began from the start of the infusion to enhance this state and the counteraction induced by the infusion was obliged to overcome both these components of vasoconstriction to exert a visible effect. The often noticed temperature-increase reaction is thus dependent on the readiness of the vascular bed of the fingers to dilatate. This predilection apparently varies with the individual.

The temperature curves registered from the fingertips in connection with noradrenaline infusion can be distributed by certain characteristics into groups representing different types of reaction.

Reaction Type I. — An initial temperature drop in the fingertips is established in this type at the beginning of the noradrenaline infusion. The temperature begins, however, to rise again as the infusion progresses. This rise is so marked in the extreme cases that the temperature ceases to rise any further when the infusion is over. But usually the temperature rises further after the infusion. The biphasic character of the thermal reaction is usually clear. In contrast, the first rise can sometimes be followed by a fall, and so on. When this happens the temperature curve is irregular in shape. A typical feature in such an instance, however, is that the temperature as a whole keeps at a fairly high level. There is a footnote to Table 3 to denote the time after the beginning of the noradrenaline infusion at which the temperature climb begins.

Reaction Type II. — The temperature falls throughout the noradrenaline infusion or, if the fingertip temperature was already near room temperature before starting the infusion, it keeps at the same low level. The temperature increase occurs after the noradrenaline infusion is complete. It may begin immediately, in which case it is denoted by 0 in the footnote, or after some time in

which case the figure in the footnote expresses the minutes between the start of the temperature increase and the termination of the noradrenaline infusion to an accuracy of 5 min.

Reaction Type III. — The finger temperature is low at the termination of the noradrenaline infusion and remains at the same

TABLE 3

The types of reaction to the noradrenaline infusion and their distribution according to Gahlen and Klüken in the total series of healthy tests subjects. A — women, B — men

A

Case No.	Noradr. type	Type of Gahlen & Klüken
1 a	III	iii
1 b	III	iii
2	III	iii
3 a	III	iii
3 b	III	iii
4	III	iii
5 a	II_{10}	iii
5 b	III	iii
6	II_{30}	i
7 a	II_5	iii
7 b	II_5	iii
8	III	iii
9 a	III	iii
9 b	III	iii
10	I_{15}	i
11 a	II_5	ii
11 b	II_{30}	ii
12	III	iii
13	III	iii
14	III	i
15	II_{10}	i
16	II_5	iii
17	III	i
18	III	ii
19	II_5	ii
20	III	iii
21	III	iii

B

Case No.	Noradr. type	Type of Gahlen & Klüken
22	II_5	iii
23	II_5	i
24 a [1]	I_{25}	iii
24 b [1]	I_{25}	iii
25	II_5	ii
26	I_{10}	i
27	I_5	i
28	II_{45}	iii
29 a	I_5	i
29 b	I_5	i
30	I_{15}	i
31	II_{20}	iii
32	II_{10}	iii
33 a	I_5	i
33 b	I_5	i
33 c	I_{10}	i
34 a	II_0	ii
34 b	II_5	iii
35 [1]	I_{15}	iii
36	I_{10}	i
37	I_{10}	i
38	I_5	i
39	I_5	i
40	I_5	i
41	I_{10}	ii
42	II_5	i
43	II_{25}	iii
44	II_{15}	i

[1] In these cases the noradrenaline dosage was not uniform.

level. No temperature rise occurs in the course of the observation period.

Table 3 gives this distribution for the series of normal subjects.

Intraindividual Variation. — The reaction type remained the same in 5 cases in repeat tests performed on 6 women. Case 5 gave a reaction of type II on the first examination, the temperature rise beginning 10 min. after the end of the noradrenaline infusion. The second test failed to elicit any temperature increase reaction and thus gave a reaction of type III. The reaction type remained unchanged in the repeat studies on men. In addition to the repeat examinations of 4 healthy men (Table 3), examinations were made twice on 3 men of the clinical series (Table 6). These examinations also gave a consistent result regarding the type of reaction in the same individual. Hence the reaction type seen in individuals at different examinations was fairly stable.

Interindividual Variation. — The reaction types established on the basis of the temperature changes provoked by noradrenaline infusion were compared with the types of Gahlen and Klüken and of Heidelmann.

The classification by Gahlen and Klüken is based on the extent to which the finger temperature follows the room temperature in a resting test subject. The finger temperature remains at a high level in homoiothermal cases despite cooling for an hour at the room temperature of 18°C. In poikilothermal cases the finger temperature drops to the room temperature and in heterothermal cases it varies between the body temperature and room temperature.

In the present investigation the test subjects had an hour to adapt themselves to the room temperature which was higher than that used by Gahlen and Klüken. However, the finger temperature prior to starting the noradrenaline infusion illustrates the behaviour of the circulation in the fingers in hypothermal conditions and the corresponding division into three types is easy to perform. Table 3 shows the division: in type i the finger temperature was regularly over 30°C, in type iii it was continuously under 25.0°C and in type ii it varied between these two.

Table 4 compares the noradrenaline types and types of Gahlen and Klüken. A high temperature in the fingers after an hour's cooling favours reaction type I and a low temperature favours reaction type III. But there are exceptions. Low finger temperatures

TABLE 4

Comparison of the types of reaction to the noradrenaline infusion (I—II—III) and the types of Gahlen and Klüken (i—ii—iii). Gahlen and Klüken's type i and ii show a fairly good correlation with noradrenaline types I and II. Gahlen and Klüken's type iii, however, is distributed between noradrenaline types II and III in the ratio 10/14. The distribution by the reaction to noradrenaline infusion divides this series into three nearly equal parts, whereas in the distribution according to Gahlen and Klüken the middle group remains fairly small.

	I	II	III	Total
i	14	5	2	21
ii	1	5	1	7
iii	③	10	14	27
Total	18	20	17	55

○ The noradrenaline dosage was not uniform in these cases.

in particular often displayed sharp temperature increase reactions of type II after the noradrenaline infusion. A reaction of type III was established in fairly few cases which had a high initial temperature. Reaction type II predominated in heterothermal cases which were in the minority compared with the other types.

»The acral arteriolar function» was studied according to Heidelmann in 19 normal subjects in the same conditions as the noradrenaline infusion experiments. The adaptation period of one hour was not used in this study and the 15 minutes suggested by Heidelmann was considered sufficient. Temperatures were then measured from six fingertips (the 1st, 3rd and 5th finger of both hands) and the hands were immersed up to the wrists in 15°C water for 5 min. After the water bath the hands were dried on a towel and the temperature of the same fingers was measured again. The finger temperatures were then followed at 5-minute intervals while the test subject lay on the examination table in the same position as in the noradrenaline examination. If the fingertip temperatures failed to rise spontaneously to distinctly above the room temperature within 30 min. of the water bath the subject was given 500 ml of 55°C water to drink. The water was given by tube — the subject did not use his hands and continued to lie in the same

position. The ingestion of water was completed in 5 min. and the finger temperature was then followed again at 5 min. intervals.

The mean temperature of the six fingers was calculated as a function of time and classification into Heidelmann's types was performed according to the time at which the temperature began to rise over the room temperature. The time lapse before the fingertip temperature passed the 25°C limit was the decisive criterion. In Heidelmann's arteriolar dilatation type this limit was reached in under 10 min. In the normal type the corresponding time was 10—20 min. The level was reached in 20—30 min. in the arteriolar constriction type of grade I. In the following types the finger temperature failed to show any difference from room temperature within 30 min., but after the ingestion of hot water it rose to above 25°C in the arteriolar constriction type of degree II. In the arteriolar constriction type of grade III the temperature rose slightly after the ingestion of hot water but not to 25°C.

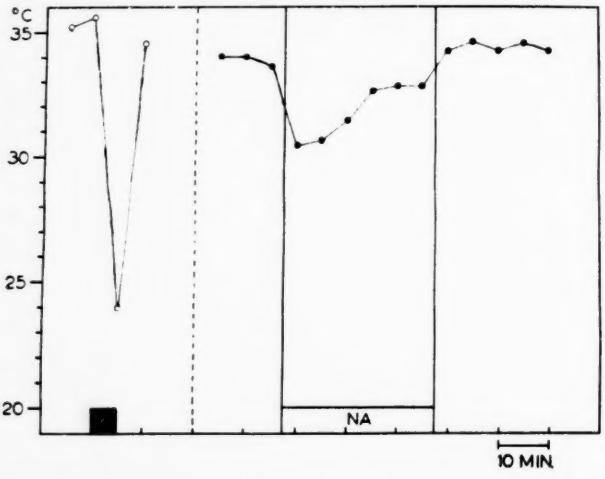

Fig. 33. — In the investigation made by Heidelmann's method the finger temperature rises spontaneously in 5 min. after a cold water bath to nearly the initial level: arteriolar dilatation type. In the noradrenaline study made on the same person the temperature changes in the fingertips accord with reaction type I. The room temperature is 23.5°C in both examinations.

Case No. 37 (a man of 31).

O—O—O Heidelmann curve;
●—●—● noradrenaline curve;
■ hands in cold water.

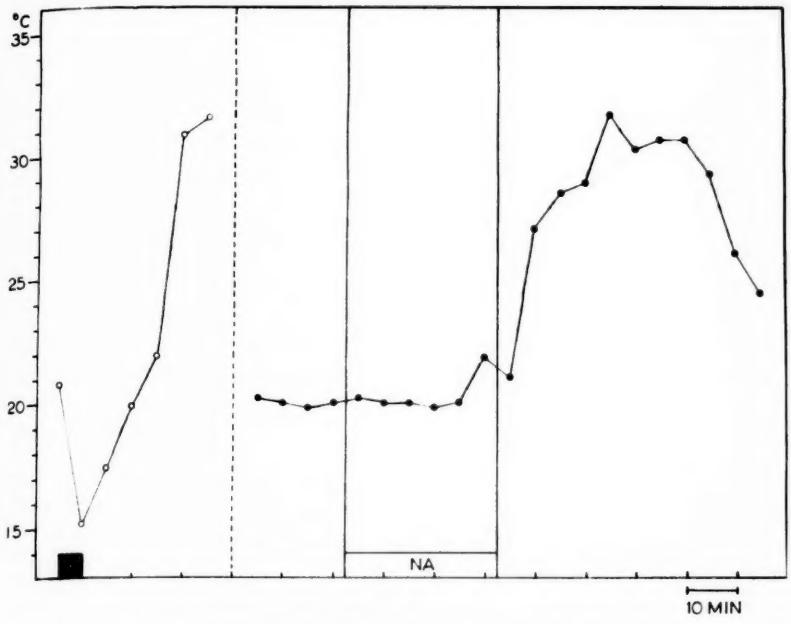

Fig. 34. — In the investigation performed according to Heidelmann the finger temperature rises spontaneously in 20 min. after a cold water bath to above 30°C: normal type. Room temperature 22.0°C.

In the noradrenaline infusion study the reaction is of type II. Room temperature 22.5°C.

Case No. 16 (a woman of 20).

O—O—O Heidelmann curve;
●—●—● noradrenaline curve;
■ hands in cold water.

Figs. 33—35 give examples of the arteriolar dilatation type, the normal type and the arteriolar constriction type of degree II. They also show the temperature curve for the fingertips of the same persons in connection with noradrenaline infusion.

The comparison between the reactions established by noradrenaline infusion and the Heidelmann's test in 19 healthy subjects is given in Table 5.

This series consisted of 6 representatives of reaction type I, 6 of type II and 7 of type III. The arteriolar dilatation type predominated in reaction type I. Reaction type II included 4 cases of normal type and 2 of arteriolar dilatation type. The most noteworthy feature, however, was that all the cases with a reaction of

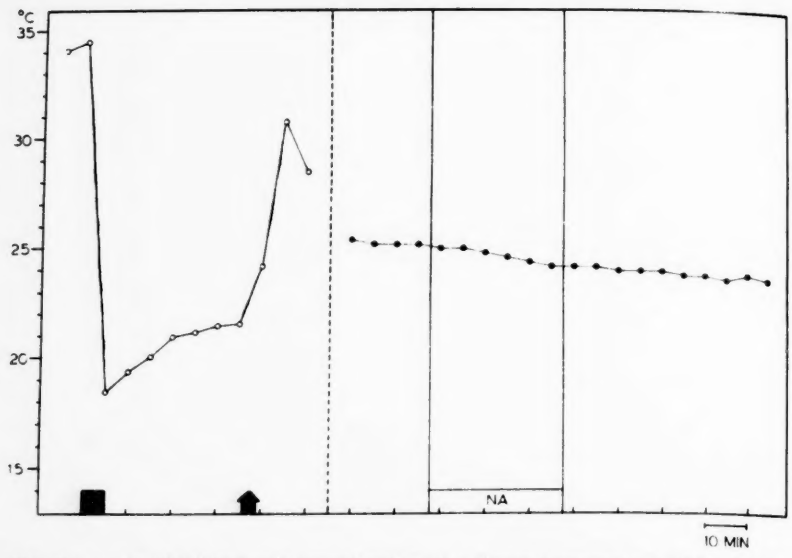

Fig. 35. — In Heidelmann's investigation the finger temperature does not rise spontaneously in 30 min. after a cold water bath to above room temperature. The rise in the fingertip temperature occurs only after the ingestion of hot water: arteriolar constriction type of grade II. Room temperature 23.2°C. No temperature reaction is established in the fingertips after the noradrenaline infusion: reaction type III. Room temperature 23.5°C.

Case No. 20 (a woman of 29).

O—O—O Heidelmann curve;
●—●—● noradrenaline curve;
■ hands in cold water;
⬟ hot water drink.

type III in the noradrenaline study belonged to the arteriolar constriction type of grade II or III in Heidelmann's study. In other words, *none of the subjects whose fingertip temperature displayed no temperature rise reaction after the noradrenaline infusion showed a spontaneous increase in fingertip temperature even after a cold water bath.* Here obviously lies the most important point of the interindividual variation in the temperature and circulation reactions in the fingers. The limit between reaction types I and II is slightly indefinite, but the boundary between types II and III appears sharper and more important for the classification. The noradrenaline infusion study and Heidelmann's study were generally made at intervals of a few days or weeks. But in cases 11, 34, 16 and 4 there was an interval of 3 years. The same

TABLE 5

THE NORADRENALINE AND HEIDELMANN TYPES IN THE GROUP OF 19 NORMAL SUBJECTS

Case No.	Noradrenaline type	Heidelmann type
38	I	Arteriolar dilatation type
40	I	Arteriolar dilatation type
27	I	Arteriolar dilatation type
37	I	Arteriolar dilatation type
30	I	Arteriolar dilatation type
10	I	Normal type
22	II	Arteriolar dilatation type
19	II	Arteriolar dilatation type
11	II	Normal type
6	II	Normal type
34	II	Normal type
16	II	Normal type
14	III	Arteriolar constriction type, grade II
17	III	Arteriolar constriction type, grade II
20	III	Arteriolar constriction type, grade II
13	III	Arteriolar constriction type, grade II
4	III	Arteriolar constriction type, grade II
18	III	Arteriolar constriction type, grade III
8	III	Arteriolar constriction type, grade III

correlation, nevertheless, was established in these cases, too. However, as mentioned before, reactions of both type II and III were demonstrated in the same subject (No. 5).

Character of the Reaction Types. — It will be seen from Table 3 that reaction type III was established in 13 out of 21 women. In contrast, no reaction of type III was established in the 23 healthy men. Reaction type III was thus fairly characteristic of women.

Further analysis of the group of women with a reaction of type III revealed that 8 of them had suffered from cold hands and felt the cold readily during wintertime. Two of the women had had urticaria due to cold in the winter (Nos. 17 and 20) and 2 (Nos. 12 and 14) reported that their fingers often turned white in cold weather. No appreciable sensitiveness to cold was reported by the women of reaction type II. For instance, case 16 whose fingers had a low initial temperature in both noradrenaline and Heidelmann's studies said that her hands were always cool but that they never felt cold even in very cold weather. Case 10, who responded

in conformity with type I, said that as far as her hands were concerned she endured cold weather very well.

There was not a single case in the male group troubled regularly by coldness and freezing of the hands. Two of them reported, however, that their fingers sometimes turned white in cold weather (Nos. 34 and 44). All the men of reaction type I said that they had warm hands and tolerated cold well.

There were no marked differences in the central effects of noradrenaline in the different reaction types. The mean blood pressure changes in women in type II were 117/79—148/97—115/76 and in type III 111/73—136/87—111/71. In men mean blood pressure changes in reaction type I were 118/79—148/92—120/77 and II 111/77—147/92—112/73. Correspondingly, the mean heart rate changes in women in type II were 66—55—74 and III 68—56—71, and in men in type I 60—49—66 and II 62—51—66.

CLINICAL OBSERVATIONS

The changes in the skin temperature of the limbs provoked by noradrenaline infusion were also studied in a small clinical series. The results obtained in the different groups were so consistent and, on the other hand, so clearly divergent that they seemed to be worth reporting.

Obliterative Arterial Diseases of the Extremities. — This group consisted of 8 men, 6 of them with arteriosclerosis and 2 with Buerger's disease (Nos. 47 and 51). All of them had obliterative arterial changes in both lower limbs and one (No. 46) also in one upper limb (the right arteria radialis pulse was hardly countable at all). A total of 11 noradrenaline infusions was given to these subjects. The temperature changes in both the upper and lower limbs were measured. There was a total of 9 sympathectomised lower extremities in this series which were not taken into consideration. The results are given in Table 6.

The toe temperature remained low throughout the investigation in all except one case. An incipient temperature rise in the toes of the left foot was established in case 46 in the final phase of the noradrenaline infusion. The temperature increased further after the infusion was over. The results in the fingers were fairly uniform and they showed a pronounced vasodilatation tendency in all the

TABLE 6

The results obtained in the group of patients with obliterative arterial diseases. The reaction type established in connection with the noradrenaline infusion is given for the fingers. In the forearms, legs and thighs there is no temperature increase during the noradrenaline infusion. All the subjects of this group are men. Cf. Tables 1 and 2

Case No.	Diagnosis	Fingers	Forearms		Legs		Thighs	
			Right	Left	Right	Left	Right	Left
45	Ao	I	—	—	—	—	—	—
46	Ao	I	—	—		—		—
47	To	I	—	—				
48 a	Ao	II	—	—	—	—	—	—
48 b		II	—	—	—		—	
49 a	Ao	II	—	—	—	—	—	—
49 b		II	—	—	—		—	
50 a	Ad	I	—	—	—		—	
50 b		I	—	—				
51	To	I	—	—		—		—
52	Ao	I	—	—	—	—	—	—

Ao = Arteriosclerosis obliterans
Ad = Arteriosclerosis diabetica
To = Thromboangitis obliterans

cases. The reaction in the fingers was of type I in 6 subjects and of type II in 2 subjects. In the type II cases the temperature climb always began immediately after the noradrenaline infusion. It is worthy of special note that the temperature changes in the fingers of the right hand in case 46 were exactly the same in type as those in the fingers of the left hand although the right upper extremity displayed distinct symptoms of obliterative arteriosclerosis. The temperature rise in the fingers of the right hand was in fact a little slower and less steep than that in the left hand. No temperature increase during the noradrenaline infusion was established in the proximal parts of the limbs.

Raynaud's Disease. — The subject was a woman of 43 (case No. 53) whose fingers 4—5 months previously had begun to turn white periodically. These spells soon began to increase in frequency and were associated with pain in the fingers. The condition was readily relieved by cold and nervousness. The spells soon began to occur several times a day and finally the pain in the fingertips

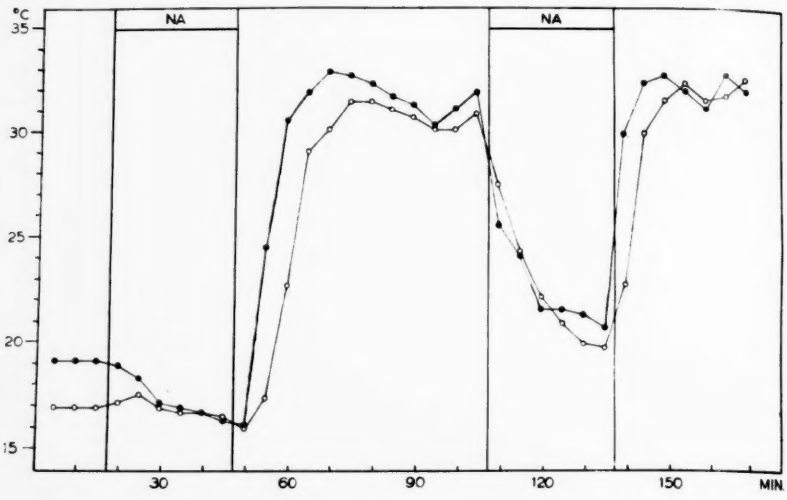

Fig. 36. — Raynaud's disease. Vigorous warming occurs in the fingertips after the noradrenaline infusion and the fingertip temperature remains high until the next infusion given 60 min. after the termination of the first infusion. During the second infusion the fingertip temperature drops sharply, but rises again immediately after the infusion is over. Reaction type II.

Case No. 53 (a woman of 43). Room temperature 21.5°C.

O—O—O right thumb; ●—●—● right little finger.

was almost constant. All the fingers were affected. By the time she was admitted to hospital a gangrene had developed at the tips of the forefinger and middle finger of her right hand. Fig. 36 shows the temperature fluctuation in the thumb and little finger of the right hand in connection with the noradrenaline infusion. The patient was given two successive noradrenaline infusions with a 60-min. interval.

Before the noradrenaline infusion the patient's hands were bluish-white and very clammy. Because of the evaporation of moisture the fingertip temperature was very low, considerably below the room temperature of 21.5°C. After the first noradrenaline infusion the finger temperature began to rise rapidly and sharply and the hands changed to warm red in colour. The warmth in the fingers persisted until the second noradrenaline infusion. When this began the finger temperature fell again rapidly and the hands became pale. Then a temperature increase followed immediately and also this time it appeared to be fairly persistent. The patient

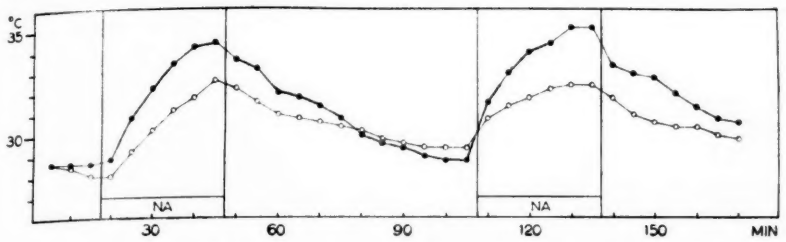

Fig. 37. — Raynaud's disease. A sharp temperature increase occurs in both forearms during both noradrenaline infusions. The temperature begins to return to its initial value immediately after the termination of the infusion. Case No. 53 (a woman of 43). Room temperature 21.5°C.

O—O—O right forearm; ●—●—● left forearm.

had a very pleasant feeling in her hands after the noradrenaline infusion.

A sharp temperature rise occurred in this case in the forearms during both noradrenaline infusions, as can be seen in Fig. 37.

Acrocyanosis. — There were 2 women (Nos. 54 and 55), aged 33 and 27, who for as long as they could remember had suffered from cold, clammy and bluish hands. Both had pronounced cyanosis in all the fingers and to some extent also on the ulnar surface of the hands. The cyanosis was most marked in the end phalanges of the digits.

The attention was attracted in both these patients by the complete disappearance of the symptoms when they were recumbent with their upper limbs in the horizontal plane. After an hour in a supine position the finger temperature was 33°C in both cases and the hands dry and perfectly normal in colour. In case 55 the mean finger temperature fell to 25.3°C after 15 min. of standing with the upper limbs hanging down. When the patient had lain down for 10 min. after this the mean finger temperature was 30.8°C and after standing again for 5 min., 27.5°C.

With the patients in a recumbent position during the noradrenaline infusion, both cases first showed a sharp fall in the finger temperature and then a rise which began while the infusion was still in progress. After the noradrenaline infusion there was a new rise to a higher level. The reaction was thus in both cases very typically of type I. Case 54 was also examined by Heidelmann's method on different days both in a recumbent position and standing. In the

recumbent position a spontaneous temperature rise occurred 25 min. after a cold water bath, but when the patient stood up the fingertip temperature did not rise until after the ingestion of hot water.

No temperature increase during the noradrenaline infusion was demonstrated in the forearms in either case.

Comments. — A definite and marked tendency to vasodilatation was established in the fingers of all the cases and in the toes of one case with obliterative arterial disease in the extremities — with the exception of one case, only the lower limbs were affected in a clinically demonstrable degree. The drop in the finger temperature changed to a vigorous rise in the latter phase of the noradrenaline infusion or after its termination. This has already been stated to illustrate at least to a considerable extent the opening of arteriovenous shunts in the fingertips. Popoff (145) claimed that arteriovenous shunts which remain open permanently have a prominent role in the pathogenesis of peripheral obliterative arterial diseases. He found that active, contractile shunts changed in these diseases (arteriosclerosis and thromboangitis obliterans) into permanently open rigid tubes in which the blood flows unregulated from the arterioles direct into the venules. This view was supported by Harpuder *et al.* (95) who established a high oxygen, low carbon dioxide and relatively high lactic acid content in the venous blood from the periphery of the affected limb.

In the case with Raynaud's disease noradrenaline had a pronounced vasoconstrictive effect on the blood vessels of the fingers, but it was very distinctly noticeable that the vasospasm of the fingers relaxed rapidly after the noradrenaline infusion, and that for a fairly long time. It is interesting to note that the temperature rise in the fingers after serotonin infusion has been shown to begin distinctly later in patients with Raynaud's disease than in normal subjects (93).

In the cases of acrocyanosis the noradrenaline study suggested a well balanced arteriolar activity when the limbs were placed horizontally. At least there was nothing indicative of a pronounced tendency to arteriolar constriction. The impression gained was that the circulatory disturbance in the hands in these cases depended entirely on orthostatic factors and there was a disequilibrium between the arterial and venous sides at the arteriolar-

venular level. When the limb hung vertically there was obviously a stasis in the venules and the superficial vein plexuses of the fingers, resulting in cyanosis. Stasis, on the other hand, gave rise to a reflectory tendency to reduce the volume of blood coming from the arterial side, possibly with the aid of a venivasomotor reflex (80, 22). This led to arteriolar constriction and to the coldness of the distal parts of the limb. The primary cause for this circulatory disorder must consequently lie on the venous and not on the arterial side.

DISCUSSION

It has been established in the literature that noradrenaline causes vasoconstriction in the cutaneous blood vessels. The vasoconstrictive effect of noradrenaline on the circulation in the hand has been demonstrated in both plethysmographic and calorimetric studies with an intravenous dose of from 5 to 30 μg/min. This obviously direct vascular effect of noradrenaline was elicited in the tests performed on the present series as a drop in the acral skin temperature of the limbs during an intravenous infusion of noradrenaline. The dose employed, 0.2 μg/kg/min., was similar to the average dosage used in previous investigations. In addition to the vasoconstrictor reactions, special interest was aroused by the renewed rise in the fingertip temperature in the middle of the noradrenaline infusion and by the sharp temperature increases that occurred in the fingertips after the end of noradrenaline infusion even when a strikingly low temperature had been recorded in the fingertips prior to starting the noradrenaline infusion. These vasodilator reactions must be considered not only in relation to the effect of noradrenaline but also in relation to the test subject because these reactions show considerable variations in different individuals.

Vasodilator reactions following noradrenaline infusion have been established earlier. One of them is flushing of the face which is very pronounced after an adrenaline infusion (14, 89) but much fainter after a noradrenaline infusion (19). The flushing phenomenon can be seen after paroxysmal hypertensive attacks in cases of pheochromocytoma (115). Swan (161, 162) established a distinct after-dilatation in the circulation of the hands following an adrenaline infusion. He associated this reaction with the flushing phenomenon and regarded it as central in origin. He attributed the after-dilatation to the inhibition of the sympathetic nervous impulses coming

to the hand. This inhibition was possibly a result of a transmission disturbance in the sympathetic ganglia provoked by adrenaline. This argument was supported by the fact that reaction demanded an intact sympathetic innervation in the limb and occurred in connection with intravenous but not intra-arterial infusion. No after-dilatation following noradrenaline infusion was established by Barcroft and Swan (19) with a dosage of 20 μg/min. Their infusions, however, only lasted 3 min.

The inhibitory effect of adrenaline on the transmission in the sympathetic ganglia has been demonstrated many times. Kappert and his co-workers (117) found that noradrenaline, too, administered in an intravenous infusion lowers the neurogenic sympathetic tonus. Tetraethylammoniumchloride, which blocks the vegetative ganglia, causes an elevation and not a fall in blood pressure during noradrenaline infusion. This is due to the blocking of the parasympathetic tonus which has increased during the noradrenaline infusion while the blocking of the sympathetic tonus reduced reflectorily during the noradrenaline infusion has a much smaller effect on the blood pressure. According to these authors, the increase in blood pressure provoked by noradrenaline infusion arises from direct stimulation of the vasoconstrictive receptors and so noradrenaline increases the humoral aspect of the vascular tonus. They hold that the neurogenic vascular tonus, on the other hand, is reflectorily reduced during noradrenaline infusion. This neurogenic counter-effect can be seen in *e.g.* the bradycardia which occurs during the noradrenaline infusion.

De Langen (126) studied the effect of noradrenaline on the peripheral circulation *e.g.* by capillary microscopy and came to the conclusion that the effects of intra-arterial and intravenous noradrenaline injection differ. Intra-arterial injection causes simple vasoconstriction but intravenous injection has a dual effect, narrowing or closing of the capillaries and opening of arteriovenous shunts. He concluded that the effect on arteriovenous shunts might be due to the direct influence of noradrenaline on the »tensoreceptors» in the sinus caroticus (102) which provokes reflectorily a weakening of the sympathetic tonus.

Various opinions have been proffered concerning the effect of noradrenaline on the circulation of blood in the proximal parts of the limbs. A reduction in flow in the forearm has been demonstrated

plethysmographically during intravenous noradrenaline infusion (49, 21). The same effect was shown in the circulation of the leg (128). However, Barcroft and Konzett (18) established a sustained increase in the circulation of some subjects during noradrenaline infusion. This phenomenon was demonstrated in several subjects of the series of Barcroft *et al.* (17). In the rest of the cases the circulation remained unchanged during noradrenaline infusion. The noradrenaline dosages used by these authors for the intravenous infusions were 10 and 20 μg/min. The circulation of an intact limb diminished during an intra-arterial infusion of noradrenaline. It diminished, too, during an intravenous infusion when the sympathetic nerves of the forearm were interrupted or blocked. These workers (17) concluded that intravenous noradrenaline infusion has two antagonistic effects, a direct constrictive and an indirect dilating effect, via the sympathetic nerves. The final outcome is the resultant of these effects. This would seem to account for the diversity of results reported in the literature. The indirect vasodilating effect of noradrenaline, in their opinion is a central effect possibly transmitted via the vasomotor centre or baroreceptors.

The vasodilator reactions in both distal and proximal parts of the limbs have, thus, been quite similarly interpreted in the literature. In the present study, however, the vasodilator reactions in the different parts of the limbs differed essentially from each other. The sharp temperature increases in the acral parts of the limbs occurred chiefly after the termination of the noradrenaline infusion, and in the proximal parts of the limbs the temperature increases occurred during the noradrenaline infusion and began to disappear immediately the infusion was completed.

Barcroft and his co-workers (17) claimed that the vasodilatation in the forearms in connection with intravenous noradrenaline infusion takes place in the muscles because the influence of noradrenaline on the cutaneous blood vessels is assumed to be always vasoconstrictive (18). This view is based, however, chiefly on the pallor seen in the face during the noradrenaline infusion and on the results from investigations of the circulation in the hand. The effect of noradrenaline on only the skin circulation of the forearm has not been studied. The temperature climb in the skin of the forearm, established many times in the present investigations, does not rule out the possibility that it might be due to the con-

duction of heat from the underlying muscles (88). However, it must be noted that the skin of different areas such as the distal and proximal parts of the limbs has been demonstrated to differ considerably, even qualitatively, in its circulatory reactions.

In the lower limbs, an increase in the blood flow of the proximal parts during the noradrenaline infusion has not been established before. The present investigations have proved that an increase in the skin temperature of the proximal parts of the limbs during noradrenaline infusion is common just in the lower limbs, in the legs and especially in thighs. The findings indicate, furthermore, that this reaction is common in women but rare in men. Obviously, a diversified hemodynamic process is involved, one in which the above-mentioned dual effect of intravenously administered noradrenaline is one factor and general blood distribution processes are additional factors. The »borrowing-lending» principle (13) could be applied here by assuming a redistribution of blood between the distal and proximal parts of the limbs due to the noradrenaline infusion. The difference between men and women may have a hormonal basis. However, seeking for the possible explanation, dissimilar acclimatisation because of clothing differences is worth remembering. This might affect the mutual roles of the distal and proximal skin areas for the thermoregulation of the body.

The tests established the same range of variation in skin temperature in the acral parts of both the upper and lower limbs. However, viewing the series as a whole, a considerable difference was noted between the fingers and toes because the temperature increase reactions were very rare in the toes. It has already been mentioned that a considerably higher vasomotor tonus prevails in the toes than in the fingers in normal conditions. Furthermore, the blood vessels of the toes are more sensitive to vasoconstrictive effects than those of the fingers (150), and the vessels of the toes have a higher power of resistance than the finger vessels to vasodilating effects (114, 7).

The typical temperature changes in the acral and proximal parts of the limbs differed materially from each other. The wrists and the ankles constitute the boundary zone between these regions. Temperature changes in them followed those in the distal parts. It is, however, very probable that the wrists and ankles merely reflect the changes in the circulation in the distal parts which are

influenced by the heat of the blood returning through the superficial veins (88).

Special attention was attracted by the interindividual differences in the thermal reactions of the fingers to noradrenaline infusion. The correlation with Heidelmann's types was close in the respect that the subjects who showed an increase in the finger temperature towards the end of or after the noradrenaline infusion also displayed a spontaneous temperature increase after a cold water bath in Heidelmann's study. Heidelmann regarded the individual variation as an indication of the differing acral arteriolar function which seemed to be dependent on hormonal factors. On the basis of a clinical examination he established a correlation between the acral arteriolar function and the activity of the pituitary gland (98). The reaction type which is predisposed to vasodilatation represented, in his opinion, vigorous activity of the anterior lobe of the pituitary gland and the vasoconstrictive type represented, conversely, slow activity of the anterior lobe of the pituitary. Heidelmann further noted that the arteriolar dilatation type was inclined to be associated with acute inflammatory diseases and the arteriolar contriction type with chronic proliferative diseases. Results obtained from sensibilisation studies on rabbits indicated a similar behaviour: the acral arteriolar function changed during the course of the sensibilisation from arteriolar dilatation type to constriction type (99).

According to Gahlen and Klüken (78) the fingertip temperature of adults tends to follow either the internal or external temperature. There were two mean temperature maxima, 31° and 20°C, for the fingers in a large investigation series. This tendency determines 2 basic types. The third type which is more infrequent comes between these two. Heidelmann stated that the re-warming of the fingertips after a cold bath, which he regarded as the indicator of the arteriolar function in the fingers, is not governed by the basic temperature of the fingers. The present findings concerning the temperature rise reactions of the fingers to noradrenaline infusion point to the same direction; vigorous temperature increases were stated after the noradrenaline infusion in many subjects with a low initial finger temperature. It seems that the properties of the circulation in the fingers which form the basis for the type classification introduced by Gahlen and Klüken, on the one hand, and

by Heidelmann on the other hand, are not identical. In the classification by Gahlen and Klüken the issue involved the adaptation of the circulation in the fingers to constant conditions, whereas changing conditions were involved in Heldelmann's test and also in the noradrenaline infusion study. Thus, the results obtained from these investigations obviously reflect better the circulatory properties in »functional» circumstances.

SUMMARY

The effect of intravenous noradrenaline infusion on the skin temperature in human limbs was studied. A 30-minute noradrenaline infusion was used, dosage 0.2 μg/kg/min. The test subject lay in a supine position in a room temperature of 22—23.5°C.

In the fingers the main effect of noradrenaline infusion was an increase of the vasoconstrictive tonus. In subjects with a high initial temperature in the fingers it was manifested as a temperature drop in the fingertips. In those with a low finger temperature before the start of the infusion it was seen as a weaker temperature rise in the fingertips in connection with reactive hyperemia during the noradrenaline infusion than prior to it.

Recovery from this primary reaction could occur in different forms. In some cases the temperature decrease in the initial stage of the noradrenaline infusion was followed by a renewed rise in temperature while the noradrenaline infusion was still in progress. This was regarded as a secondary phenomenon and explained as a neurogenic weakening of the sympathetic vasoconstrictor tonus released reflectorily by the sustained intravenous noradrenaline infusion. This weakening must have been so marked that the primary, direct vasoconstrictive effect of noradrenaline did not offset it.

In the subjects whose fingertip temperature fell throughout the noradrenaline infusion a large temperature rise could occur in the fingertips after the infusion or the temperature could remain at the same low level. The temperature increase reaction could also occur in fingertips in which the temperature was at a minimum, *i.e.* room temperature, before starting the infusion. The temperature increase reaction following the noradrenaline infusion was also attributed to the reflectory weakening of sympathetic tonus which in these cases was elicited only after the direct vasoconstrictive effect of noradrenaline had ceased.

The temperature reactions in the fingers were divided into three types:

Reaction type I: The fingertip temperature drops at the beginning of the noradrenaline infusion but begins to rise again while the noradrenaline infusion is still in progress.

Reaction type II: The fingertip temperature falls throughout the noradrenaline infusion or remains at its initial low level. A sharp and rapid warming takes place in the fingertips after the infusion.

Reaction type III: The fingertip temperature drops during the noradrenaline infusion to its minimum level or is at that level from the outset. No temperature rise occurs in the fingertips after the noradrenaline infusion.

Fifty five noradrenaline infusions were performed on 44 healthy subjects. In the group of 21 women a temperature change of type I was established only once; type II occurred 9 times and type III 17 times. In the group of 23 men the temperature reaction was of type I 17 times and of type II 11 times; reaction type III never occurred in men. Repeat tests performed on the same test subjects established that the variation in reaction type was fairly small within the same individual.

The noradrenaline types were compared with the types introduced by Gahlen and Klüken and Heidelmann. Some correlation was established with the types of Gahlen and Klüken, but it was rather uncertain. The correlation with Heidelmann's types, on the other hand, was more consistent. Comparison of the noradrenaline types with Heidelmann's types gave the impression that the difference between reaction types II and III in particular was sharp and fundamental.

The same temperature reactions as in the fingers were established in the toes in connection with noradrenaline infusion. A temperature increase, however, was demonstrated in the toes in very few cases only.

In the proximal parts of the limbs of many subjects the temperature rose considerably during the noradrenaline infusion. These temperature increase reactions were variable in character and often showed notable asymmetry, while the distal parts of the limbs displayed symmetric temperature reactions. Moreover,

the results obtained in the repeat tests often differed considerably from those in the first tests. The most striking feature was that a temperature increase in the proximal parts of the limbs was more common in women than in men. The most common site of reaction in both sexes was the thigh, then the leg and last the forearm.

The temperature changes in the wrists and ankles in connection with noradrenaline infusion followed the changes in the acral parts of the limbs but were appreciably weaker.

In addition to the series of healthy persons, 11 patients with peripheral vasculatory disturbances were studied in 14 examinations. The temperature reactions in the fingers of men with obliterative arterial diseases in the lower extremities were chiefly of reaction type I. In a woman with Raynaud's disease noradrenaline provoked a pronounced vasospasm which relaxed immediately after the noradrenaline infusion. The fingers remained warm and symptom-free for more than an hour after the noradrenaline infusion. Two acrocyanotic patients gave a reaction of type I. Their symptoms were shown to be dependent on orthostatic factors and the disturbance seemed to be located primarily on the venous side at the venular level.

APPENDIX

TABLE 7

The test subject group of healthy *women*. The table shows the age of the subjects and the blood pressure and heart rate changes established in connection with the noradrenaline infusion. The values were determined prior to the noradrenaline infusion, in its terminal phase and some 30 min. after it had been completed

Case No.	Age	Blood pressure			Heart rate		
1 a	24	120/75	135/80	110/75	80	64	84
1 b		105/60	125/80	105/55	78	60	84
2	24	110/70	140/90	120/70	62	48	72
3 a	26	105/75	130/90	110/70	70	56	76
3 b		100/70	120/75	95/55	68	54	76
4	21	105/70	120/80	100/70	64	56	72
5 a	22	115/75	145/100	115/70	64	50	72
5 b		120/75	150/95	120/75	62	64	72
6	23	125/85	150/95	125/85	68	60	72
7 a	22	135/85	150/95	130/85			
7 b		stellate block					
8	24	120/80	145/90	115/80	84	69	94
9 a	22				78	60	78
9 b		105/70	110/80	105/75	75	62	84
10	31	120/80	145/90	115/75	80	56	86
11 a	21	115/80	145/100	110/75	66	54	75
11 b		110/80	160/105	105/75	65	50	70
12	19	105/80	120/80	110/80	50	48	56
13	25	130/80	155/95	130/80	78	60	82
14	31	100/70	140/90	100/70	44	38	50
15	59	140/85					
16	20	115/70	140/95	115/70	82	72	92
17	30	120/80	150/100	125/75	78	58	86
18	24	105/65	145/90	100/60	64	58	70
19	20	105/75	145/90	105/75	52	42	60
20	29	120/80	150/90	125/80	62	55	62
21	22	110/70	140/90	110/70	56	48	60

TABLE 8

The test subject group of healthy *men*. The table shows the age of the test subjects and the blood pressure and heart rate changes established in connection with the noradrenaline infusion. The values were recorded as in Table 7

Case No.	Age	Blood pressure	Heart rate
22	21	120/80 160/90 120/70	54 42 56
23	26	105/75 135/80 115/70	60 48 67
24 a 24 b	54	changing dosage	
25	18	105/70 140/85 110/70	60 46 62
26	42	135/80 180/100 130/75	68 50 70
27	34	105/75 140/85 110/75	60 40 64
28	31	120/80 145/90 115/80	56 46 64
29 a	18	120/80 145/90 130/80	62 56 60
29 b		120/75 155/95 125/75	60 52 60
30	22	125/85 140/100 125/80	58 52 75
31	21	115/80 175/100 125/80	70 52 74
32	20	100/70 150/100 100/70	62 54 68
33 a	20	140/85 155/90 140/80	64 50 64
33 b		120/80 145/90 120/80	60 50 66
33 c		115/75 145/85 115/75	58 50 62
34 a	28	115/80 135/85 110/70	76 70 76
34 b		100/70 125/85 100/65	66 50 68
35	25	changing dosage	
36	22	120/85 140/90 120/85	52 38 60
37	31	100/75 130/85 100/75	52 48 58
38	26	105/75 130/90 110/80	56 43 60
39	21	125/85 165/105 125/85	66 60 76
40	27	110/75 140/80 115/60	74 49 85
41	19	110/70 160/105 110/70	52 44 58
42	23	110/75 170/110 110/70	56 40 70
43	22	120/85 150/95 120/80	60 58 60
44	59	115/80 130/90 110/80	66 58 60

TABLE 9

The clinical series. The table shows the age, sex and diagnosis of the circulatory disturbance of the test subjects and also the blood pressure and heart rate changes established in connection with the noradrenaline infusion. The values were recorded as in Table 7 and 8

Case No.	Age	Sex	Diagnosis	Blood pressure			Heart rate		
45	55	male	Ao	155/80	220/85	130/70	62	48	66
46	48	male	Ao				70	60	78
47	45	male	To	130/80	160/85	120/75	70	46	70
48 a	56	male	Ao	180/100	200/100	140/90	74	64	74
48 b				170/90	195/90	155/90	76	67	78
49 a	71	male	Ao	150/70	175/95	160/80	68	67	72
49 b				160/70	210/80	165/70	78	74	80
50 a	38	male	Ad	130/70	180/90	115/70	80	62	80
50 b				140/80	200/70	135/80	74	68	80
51	34	male	To	115/80	145/70	120/80	76	54	92
52	50	male	Ao	130/85	165/85	125/75	77	64	84
53	43	female	MR	145	185	145			
54	33	female	Ac	100/75	125/80	95/70	74	44	78
55	27	female	Ac	115/75	130/80	120/60	68	52	70

Ao = Arteriosclerosis obliterans
Ad = Arteriosclerosis diabetica
To = Thromboangitis obliterans (Bürger's disease)
MR = Raynaud's disease
Ac = Acrocyanosis

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